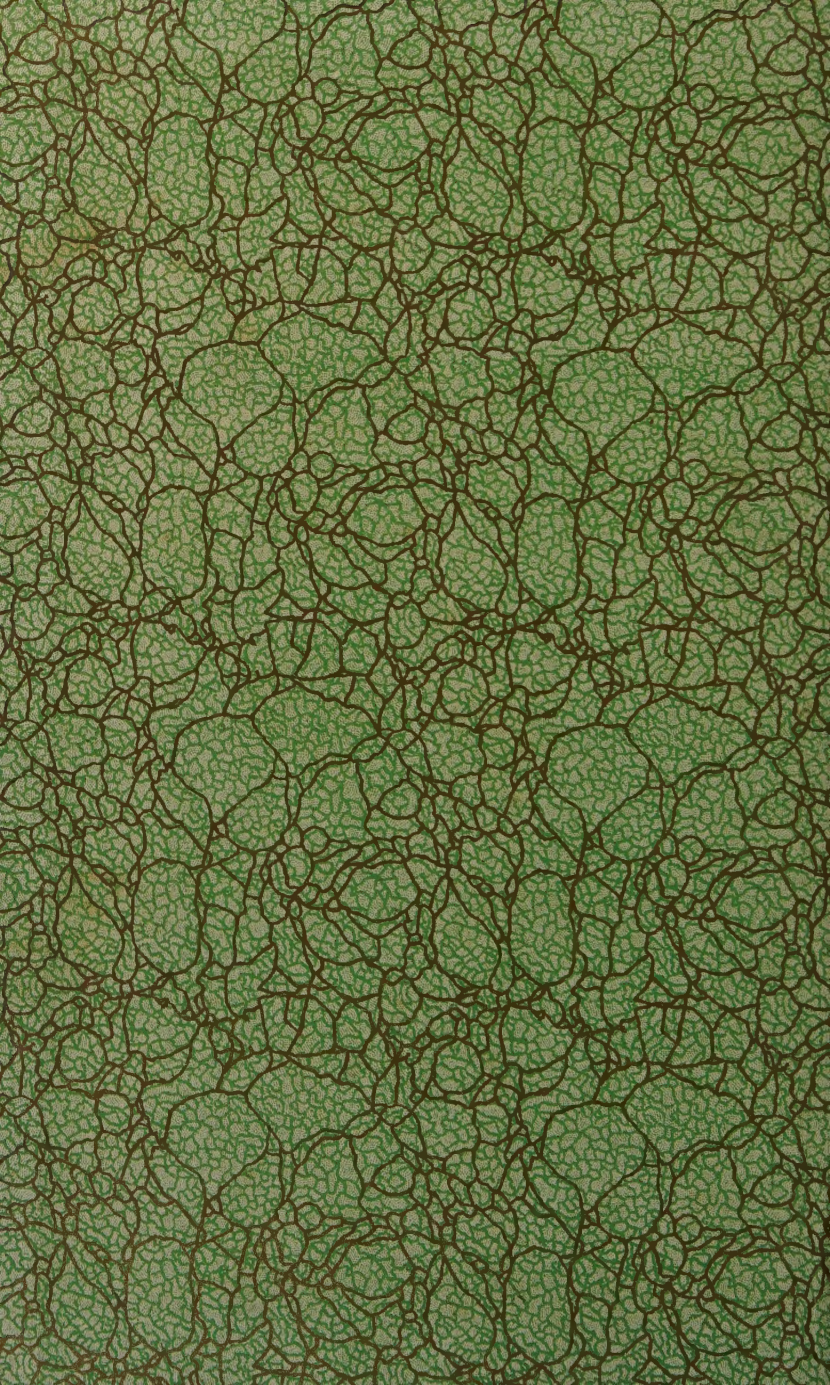
A MANUAL OF BIOLOGICAL THERAPEUTICS



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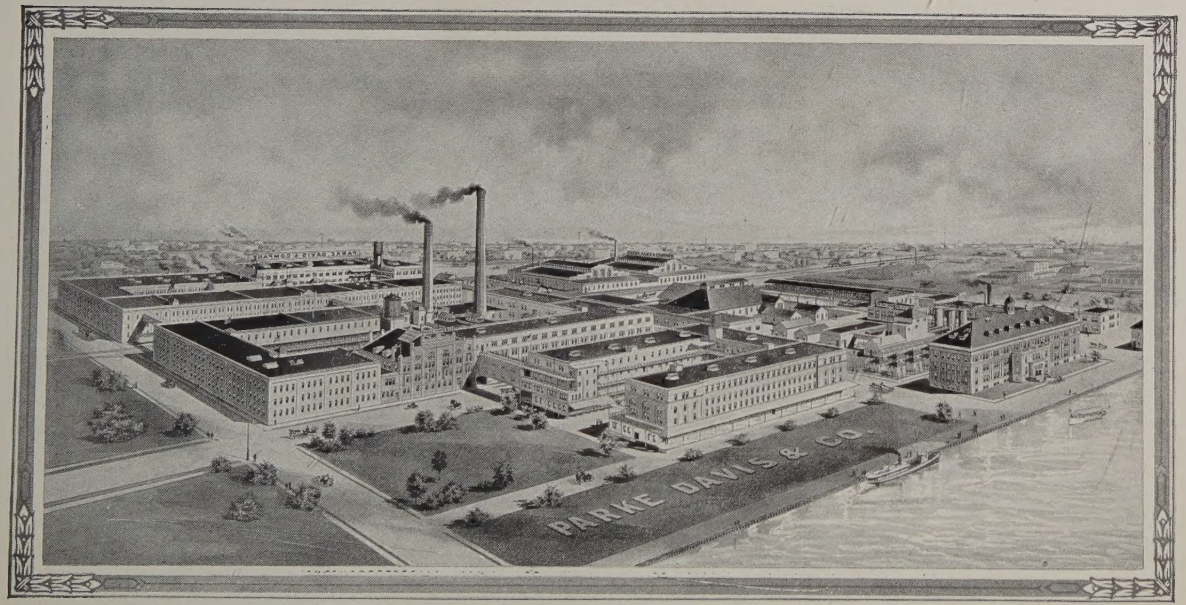

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A Manual of Biological Therapeutics

SERA
BACTERINS
PHYLACOGENS
TUBERCULINS
GLANDULAR EXTRACTS
TOXINS, CULTURES, ANTIGENS, ETC.

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1914

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A Manual of Biological Therapeutics

Section 1.

BIOLOGY.

Biology (Greek,—βιος, life; λογος, discourse) has only one true meaning—*i.e.*, its literal one, which is the science of life. In other words, it is the study of the action of life upon matter.

Man, even in his most primitive state, is gifted with the faculty of observation and has separated living matter into its two great divisions of plants and animals, and these again into tree, shrub, and herb, bird, beast, and fish; and in so far as he was able to do this he was to that extent a biologist. Two classes of naturalists were thus produced: botanists and zoölogists.

Going back to the years 499-120 B. C. and scanning Greek history, we find this division arising; for on the one hand we observe Hippocrates studying the human body and discarding the old theory which attributed disease to the wrath of the gods, and Aristotle beginning the classification of animals and speculating as to the differences between and the relative value of life in animals and life in plants. On the other hand we have Theophrastus classifying over 500 different kinds of plants as trees, shrubs and herbs.

THE DAWN OF ANATOMY.

Here we see the anatomist arising, and during the years A. D. 70-200 Pliny, the zoölogist, and Galen began the study of the component parts of a living organism, by describing two sets of nerves and proving that the arteries contain blood. During the Middle Ages all science seemed lost in the glamor of alchemy, and little or no progress was made with the study of biology until the sixteenth century. Then Vesalius made some advances in the study of anatomy, and Gesner began the formation of a botanical garden and a zoölogical cabinet. Cæsalpinus followed and made the first systematic classification of plants on Gesner's plan. Each of these pioneers of the sixteenth century had sketched out a rough plan of classification, so that botany, zoölogy and anatomy, the three subsciences of biology then extant, were beginning to assume a scientific aspect.

In the seventeenth century progress was accelerated. Fabricius Aquapendente discovered valves in the veins, and Harvey discovered the mechanism of the circulation of the blood, and thus a new branch of the science of anatomy was opened up. From that time biology must be regarded as composed of the two subsciences of morphology and physiology, morphology being concerned with the analysis of a living organism with its parts,

and phsyiology with living matter in action and the functions of the parts described. Harvey, furthermore, commenced the study of embryology, asserting that all animal life is produced from the ovum. Gaspard Aselius discovered the lacteal vessels which aid in the work of absorbing fat for the blood, and Rüdbeck discovered the lymphatics.

THE APPLICATION OF THE MICROSCOPE.

Malpighi now took up the microscope, and applied it to the study of physiology, finding air cells in the lungs and the Malpighian layer in the skin. With Grew he discovered the cellular structure of plants and the stomata in leaves. Ray and Willoughby then classified the whole animal and vegetable kingdoms and thus laid the foundations of the study of anatomical classifications.

In the eighteenth century the advance was even more rapid. During this period Boerhaave began to create the science of organic chemistry, the importance of which to biology is readily understood when we notice the fact that he himself analyzed milk, blood, etc., and showed that animal life can be sustained only by the absorption of organic compounds. Dr. Haller, of Göttingen, worked on the subjects of muscular irritability and the circulation of the blood, thus inaugurating the work that was later continued and extended by

John Hunter while involved in the study of comparative anatomy. The geographical distribution of animals upon the face of the earth was now added as a branch by Buffon, and then arose Linnæus, who invented a marvelous classification of plants and animals, founding the artificial or Linnæan system of anatomical classification. Again, Palissy the Potter originated in the eighteenth century the theory that fossils are authentic traces of extinct life, and so laid the foundation of the science of paleontology. Wolff further emphasized Harvey's theory of the development of animal life from the ovum.

THE ADVENT OF HISTOLOGY.

The nineteenth century opened with the work of Jussieu, who founded the natural system of botany, while Cuvier followed in the classification of animals. Bichat proceeded from the study of organs to the study of tissues, and so founded the science of histology. Then followed Sprengel, who worked on the fertilization of plants by insects. Next came Lamarck, who once again raised the question of evolution through the gradual development of organs by reason of use or disuse through environment, and who was perhaps the first to employ the term "biology." Von Baer followed up the work of Wolff and placed embryology upon a sound footing. Then Schleiden

in the botanical and Schwann in the zoölogical aspects of histology resolved living organisms into cells, so founding the cellular theory. Dujardin and Van Mohl further resolved cells into protoplasm, while Virchow applied the cell theory to physiology and pathology, and Bernard applied the knowledge of the protoplasm to the study of the functions of organ, tissue, and cell. In the second half of the nineteenth century Darwin and Russel Wallace simultaneously developed the evolutionary theory by their hypotheses of natural selection or survival of the fittest. This theory, having given an apparently reasonable explanation of biological development, seems to justify the general conception of evolution. It has therefore been adopted in sociology, which must be considered as related to biology, and has led to the development by Galton of the theory of eugenics which seeks to elucidate all those agencies affecting racial qualities. Prominent with Darwin and Russel Wallace as pioneers in the evolutionary theory were Haeckel and Huxley.

NATURAL SELECTION.

The doctrines of the struggle for existence and natural selection led to the science of selective breeding, of which Darwin made such good use. Then again the study of medicine, the demand for new drugs, reacted upon bot-

any and induced the cultivation of useful herbs. Further, the idea of natural selection or the survival of the fittest caused a new view to be taken of the study of mankind.

Pasteur developed the study of biology to a knowledge of the microbes of chicken-cholera and silkworm disease, and now by inoculation experiments we have learned how to guard against some of the most deadly of these microscopic organisms. Thus the subscience of bacteriology was founded. From this many branches of preventive medicine have been evolved. Lord Lister applied this knowledge to surgery, and his discovery of antisepsis, together with the use of local and general anesthetics, made possible the great surgical advances of recent days.

The latest method in which biology is applied to life is as yet only in its observation stage. This is the study of the science of eugenics, or the dominant perpetuation of the qualities, inherent or hereditary, that contribute to the ideal development of the human race.

Section 2.

BACTERIA.

Bacteria are unicellular plants of varying shapes, spherical, ovoid, cylindrical or spiral. The cell consists of a mass of protoplasm with irregular spaces contained therein, and enclosed in a cell wall which appears to be a modification of the protoplasm itself but is usually not cellular. Some bacteria have the power of locomotion, derived from cilia or flagellæ which seem to project through pores in the cell walls. The classification of bacteria is based primarily on their shape. Micrococci are small spherical bacteria; when joined together in a chain they are termed streptococci. Others that grow in masses or bunches are called staphylococci. Rod-like or cylindrical bacteria are bacilli, and those in spiral form spirilla.

The connection of bacteria with certain forms of disease was conclusively demonstrated by Pasteur, though it had long been suspected that suppuration was due to the presence of organisms in wounds. The various pathogenic bacteria will be considered separately in their proper places in this book, as well as the sera, bacterins, vaccines, tuberculins and phylacogens.

IMMUNITY.

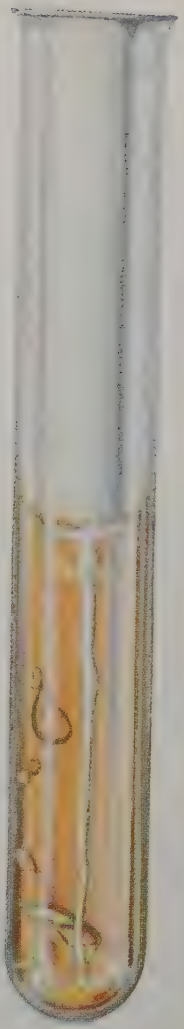
By immunity is meant non-susceptibility to a given disease or to a given organism or toxin, either under natural conditions or under conditions experimentally produced. Immunity is, in fact, of widely varying degrees and has correspondingly relative significance. So long as an organism continues to exist it must continue to adapt itself to its environment, and thus it becomes so modified as to effectually resist influences which without such modification would have brought cessation of being. The lower animals are immune to some diseases prevalent in man, and certain families have marked resistance to some diseases. These are examples of natural immunity. An individual may be immune by virtue of his being of a certain race or family. Classic is the observation, on the other hand, that one attack of certain infectious diseases affords lifelong immunity against attacks of the same disease, while in other diseases the acquired immunity is of varying duration.

THE PRODUCTION OF ARTIFICIAL IMMUNITY.

We can produce artificial immunity, either active or passive. Vaccination or the injection of bacterial toxins produces active immunity, while the injection of an immunizing serum, such as diphtheria antitoxin, confers passive immunity. In other words, in the

Bacillus typhosus, dextrose-agar stab culture.

Bacillus diphtheriae, glycerin-agar slant



Bacillus coli, dextrose-agar stab culture.

Streptococcus pyogenes, agar slant culture.

Bacillus tetani. gelatin stab culture.

first instance the patient supplies his own antibodies—active immunity; in the second instance the antibodies are supplied to the patient—passive immunity.

In active immunity, following recovery from either an idiopathic infection or an infection artificially produced, there are developed in the blood the antibodies which are inimical to the toxin or to the activity of the bacteria themselves, or which accomplish the destruction of the causative agent by the action of the phagocytes.

The normal blood serum has a powerful destructive effect upon many varieties of bacteria, and this power is found to be greatly increased in a patient who has been infected with these bacteria, either naturally or artificially.

There can be no doubt that in all cases of acquired immunity, either active or passive, the leucocytes perform a large and important part, just as they do in natural immunity. In acquired immunity the phagocytes are much more capable of absorbing or destroying bacteria than in susceptible conditions.

THEORIES OF IMMUNITY.

As to the various theories of immunity that have been formulated, we owe more, perhaps, to Ehrlich's than to any of the others. His hypothesis is known as the "side-chain" theory.

The toxic molecule is supposed by Ehrlich to consist of a haptophore group and a toxophore group. The protoplasm of living cells is supposed to consist of a central nucleus and a number of "side-chains," so called. These side-chains, or receptors, supply nutrition to the cell, and in order to perform this function they combine with or anchor molecules of nutrient material dissolved in the blood or lymph. Moreover, there are many varieties of proteins in the blood, and there are specific receptors for each of these various proteins. Upon the injection of a certain toxin into an animal, the haptophore group of the toxic molecule combines with the receptor, and the toxophore group, thus brought into communication with the protoplasm, exerts its toxic action on the central nucleus. If the dose of toxin is large, the protoplasm is fatally injured and the animal dies. When a small or non-lethal dose is injected, a certain number of side-chains necessary for the nutrition of the cell are rendered useless by combining with the toxin. The vital reaction of the tissues to injury causes other side-chains to be produced. By repeating the dose of toxin, additional side-chains are formed, and if the administration of toxin in suitable doses is continued, the protoplasmic molecule may be gradually trained to produce side-chains so rapidly that many of them become detached

from the central nucleus and float freely in the blood. They however retain still their power of uniting with the toxin molecule by means of its haptophore group, thus preventing its union with the protoplasm and rendering it virtually inert, and so they constitute the antitoxin.

NATURAL IMMUNITY.

It is assumed that the protoplasmic molecule possesses a specific side-chain for all the various toxins which might act injuriously. If a toxin be injected into an animal and the side-chains of the molecules of living protoplasm do not possess haptophore groups to fit those of the toxin, no poisoning can occur, as the toxin cannot unite with the molecule. This is the state of natural immunity.

The chemical poisons do not give rise to the formation of antitoxins, owing to the fact that these unite with all parts of the molecule.

PRECIPITINS.

Precipitins are substances formed by the injection of a protein solution, and these cause sedimentation or precipitation when the serum of the animal is mixed with a solution of the same protein as that injected.

AGGLUTININS.

Agglutinins are formed as the result of invasion or injection of bacteria; and the

serum of an individual or animal so treated, when brought into contact with the same species of bacteria, causes them to collect into clumps.

LYSINS.

Lysins are much more complex in structure than the foregoing. A combination of amboceptor and complement is necessary to produce lysin. According to Ehrlich, the production of lysins is due to the development within the serum of receptors which have the power of combining with the antigen that gives rise to them, and also combining with the complement that exists in the serum of all animals whether they are infected or not.

ANTIGENS.

Antigens are of various kinds—*e.g.*, bacteria, protozoa, animal cells, blood serum, animal proteins, and vegetable products. One observation is to be noted: if animal derivatives are injected into other animals, the two animals must not be of closely related species, otherwise no antibodies will be produced.

Section 3.

PREPARATION AND USES OF SERA.

The sera now available for therapeutic uses are of two classes, the antitoxic and the antibacterial. The antitoxic sera are obtained by repeatedly injecting animals (horses generally) with soluble toxins produced in artificial culture media by micro-organisms. The antibacterial sera are produced by injecting the animals with the actual bacterial substance of such pathogenic organisms as do not excrete their poisons.

Typical of these two classes of sera are antidiphtheric serum (diphtheria antitoxin) and antistreptococcic serum. These were also among the earliest sera to be used therapeutically; not only have they maintained their position, but their use has been successfully extended.

In our list the first three mentioned below (antidiphtheric, antitetanic and antitubercle) are properly classed as antitoxic sera; and the three following (antigonococcic, antimeningitic and antistreptococcic) as antibacterial.

As the methods of preparation of any or all of the antitoxic sera do not in any essential points differ from that of diphtheria antitoxic serum, a description of the method of prepara-

tion of the latter will suffice for all. Antibacterial sera are, of course, prepared in a similar manner, only in their case the bacteria or their cell contents are used for inoculating the animal.

CARE OF THE HORSES.

The horses chosen for serum production must be absolutely free from disease, and with this end in view they are kept for several days under close observation in a detention stable. During this time a thorough physical examination is made by a competent veterinary surgeon; this examination includes the mallein test to insure freedom of the animals from glanders. An injection of antitetanic serum is then given whereby each horse is immunized against tetanus. Not only must the horses be healthy and vigorous when inoculated; they must be kept so, and they are fed, stalled, groomed and exercised with this end unremittingly in view.

PREPARATION OF ANTITOXIC SERA.

In brief outline of the process it may be said that diphtheria toxin is first obtained from a known strain of Bacterium diphtheriæ and injected into a horse, the dose being repeated and gradually increased. These injections are carried on until the antitoxin in the horse's blood has reached a high degree of concentra-

tion. A quantity of blood is then drawn and the serum, containing the antitoxin, is decanted into suitable containers. Various animals at different times have been used in this work, but the horse is now considered to be most convenient, most easily managed, and most sensitive to diphtheria toxin, and on account of its size yields the maximum amount of blood.

THE PROCESS IN DETAIL.

The first step in the process of serum preparation is the cultivation of the diphtheria bacterium in a suitable fluid nutrient medium in order to obtain a solution containing diphtheria toxin. The strain of organism selected is chosen for its capacity to produce a powerful toxin.

Reasoning from analogy it would seem natural to suppose that the power of producing a potent toxin in the artificial culture medium would parallel the virulence of the microorganism in man or animals; such, however, is not the case. The cultures used in our laboratories for the preparation of the toxins are originally obtained from human sources, and their power of producing a highly toxic filtrate has been developed through continued long growth on the surface of fluid culture media and by repeated inoculation into guinea-pigs. It follows, therefore, that

to prepare special antitoxins for particular epidemics by the use of micro-organisms freshly isolated from cases of infection is impracticable.

THE PRODUCTION OF THE TOXIN.

The nutrient medium for the cultivation of the micro-organism is usually beef or veal bouillon. This is poured into flasks, which are then plugged with cotton and carefully sterilized by heat. The next step is to inoculate the contents of the flasks with a pure culture of diphtheria bacilli. The flasks are then placed in an incubator, where they are kept for a week to a fortnight at a temperature of 37° C. Within this interval of time the bacilli multiply enormously, and the bouillon in the flasks becomes charged with toxin. The culture thus obtained is then examined microscopically and, if found free from contamination, 0.4 per cent. of trikresol is added as a preservative. After standing for twenty-four hours the killed micro-organisms are removed from the toxin solution by filtration, and the toxin is then stored away from the action of light and heat until required for use. The filtered toxin is ultimately used to establish a condition of immunity in horses, but it is first tested on guinea-pigs to ascertain its strength before an estimate may be formed of the proper dose for the horse. The toxin is so

active that about 0.002 Cc. is fatal to a 250-gramme guinea-pig within four days.

IMMUNIZING THE HORSE.

Having determined the relative strength of the toxin it is now ready for use. To immunize the horse the injections are made subcutaneously, and with all possible precautions to preclude bacterial infection. The object is primarily to establish in the animal a "grund-immunitat" and then to increase the immunization until the antitoxin is present in the blood in high concentration. The first dose is a fraction of a cubic centimeter and is injected under the skin of the shoulder. The result of this injection is usually a rise of temperature, with symptoms of rigor, dejection and rough coat. These symptoms soon pass off, and the first dose is followed in about twenty-four hours by a larger one, and in 24 hours more by a still larger one, the gradually increased doses being continued every twenty-four to forty-eight hours, until enormous quantities can be injected. In the efforts put forth by nature to counteract the effects of the toxin, there is developed in the blood of the horse a powerful antidote or antitoxin. Usually, as the doses of the toxin are increased, the antitoxicity of the blood also increases, though this is not always the case, for occasionally horses have been treated by injections

of the toxin for as long a period as two years without producing a serum of high antitoxic potency. In most cases, however, the horse is thoroughly immunized by the end of two to four months, at which time the trial bleedings are made.

THE STRENGTH OF THE TOXIN.

In the immunizing process the maximum dose of the toxin injected into the horse is quite sufficient to kill five hundred thousand guinea-pigs of 250 grammes each, and if immunization is quite successful one cubic centimeter of the horse's blood serum will neutralize sufficient toxin to kill fifty thousand guinea-pigs of 250 grammes weight. As the disease diphtheria can be conveyed only by the living Klebs-Loeffler (diphtheria) bacillus, the horse does not contract diphtheria, for the injections consist of toxin from which the bacilli, first killed, have been removed.

THE BLEEDING OPERATION.

The operating building, separate and apart from the general stables, is of solid concrete construction with appointments similar to those of the operating-rooms of a modern hospital. It is kept thoroughly aseptic, and all instruments, vessels and apparatus are systematically sterilized after approved methods.

The immunized horse is now bled, the greatest care being taken to maintain asepsis.

A sterile cannula is inserted into the jugular vein, and a gallon or more of blood may be removed. The blood is collected in large sterile tubes or glass cylinders, which are placed in cold storage until clotting occurs. The serum is then drawn off, 0.4 per cent. of trikresol is added to it as a preservative, and it is filtered to remove particles of fibrin and to render it clear.

The serum is placed in cold storage until tests have been completed and it is required for use.

STANDARDIZATION OF THE SERUM.

Obviously, if a serum is to be of the greatest value therapeutically, there must be some means of efficiently controlling the dosage; *i. e.*, the serum must be standardized. This is done in terms of antitoxic units.

HOW THE TEST IS MADE.

To test the antitoxic value of a serum a number of guinea-pigs, each of 250 grammes weight, must be selected. Neither the guinea-pigs chosen for the test nor their parents can have been used previously for testing diphtheria toxin or antitoxin.

THE ANTITOXIC UNIT.

An antitoxic unit is to be apprehended by its effect only. It is capable of neutralizing an amount of toxin, or bacterial poison, that is

in turn measurable by its fatal effect on guinea-pigs in the presence of a standard immunity unit furnished by the United States government. The immunity unit is mixed with the toxin and administered to a guinea-pig weighing 250 grammes; sufficient toxin must be used to kill the guinea-pig, notwithstanding the protection afforded by the immunity unit. This amount of toxin (that is to say, just enough to kill the protected animal) is called the L+ dose. One *antitoxic unit* will just save the life of a 250-gramme guinea-pig when injected together with the L+ dose of toxin. As a matter of fact the L+ dose of toxin is approximately equivalent to one hundred minimum fatal doses of toxin; so an antitoxic unit will save the life of one guinea-pig exposed to the action of one hundred times the minimum fatal dose of toxin (or one L+ dose), or the lives of one hundred guinea-pigs, each exposed to one minimum fatal dose. Hence 3,000 antitoxic units, a usual therapeutic dose, will protect three hundred thousand guinea-pigs from death by *toxin*. This affords a forceful illustration of the potency of Antidiphtheric Serum, or diphtheria antitoxin.

SAFETY TESTS.

The potency of the serum having thus been ascertained it is now subjected to both ster-

ility and safety tests. The safety test is carried out by injecting the serum into guinea-pigs, the animals being kept under observation for a week or more. No serum is issued unless at the end of that time the pigs are alive and well. If the sterility test shows the absence of micro-organisms, the serum is then put into its proper containers and these are hermetically sealed.

THERAPEUTIC ACTION OF SERUMS.

Infectious diseases are caused by pathogenic bacteria which, finding a favorable soil in the patient, multiply and develop poisons or *toxins*. The patient's economy endeavors to combat the disease by developing antibodies. When that process is successful the patient recovers without treatment, or he may not become acutely ill. That is, he is immune to the disease. This is *active immunity*. In the use of therapeutic sera the active immunity in the horse is transferred to the patient and in him becomes *passive immunity*.

ANTIDIPHTHERIC SERUM.

Antidiphtheric serum has in large measure robbed diphtheria of the dread with which it was formerly regarded. In the less than twenty years since its introduction into therapeutics it has saved countless lives, and given to the medical profession a control over the

one disease of all others in the presence of which the physician had previously been all but helpless. Its value, both remedial and prophylactic, rests upon so sure a basis that it requires on our part no special commendation. It is but fitting, however, that we quote the words of an eminent American pediatrist, who says: "No tables of figures are so convincing to an individual as personal experience, and by this argument one by one the opponents of antitoxin have been converted."

THE DOSE OF DIPHTHERIA ANTITOXIC SERUM.

The dose in a case of moderate severity should be not less than 3,000 units, and in severe cases 5,000 to 10,000 units should be given at once. Even larger doses are recommended by many authorities. The tendency is toward larger dosage—even as much as 10,000 units is recommended in tonsillar diphtheria, and 25,000 units in nasal or laryngeal diphtheria. The use of 85,000 units has been reported in a single case, and doses of 50,000 units and higher are not uncommon. The conservative estimate as to dosage would seem to be never less than 3,000 units, and for cases of severe involvement 10,000 units, or even more. In cases which progress unfavorably, at least double the initial dose should be given six hours later. The same good results are not to be expected from repeated

injections at intervals as are obtained from one large dose at the outset of an attack.

If the age of the patient is allowed to have any influence on the dosage, adults should have smaller doses than children, as the prognosis in diphtheria improves with the age of the patient.

FURTHER REMARKS ON DOSAGE.

As it is impossible to know in any given case how much toxin has been, or will be, absorbed, it appears to be prudent to give more rather than less of the antitoxin than will suffice to neutralize the toxin—as evidenced by a stronger pulse, shriveling of the membrane, and less offensive odor. If the total amount of the toxin in the general circulation is not neutralized by the dose of the antitoxin given, then the uncombined toxin goes on with its destructive work; if, on the other hand, the antitoxin is in excess, no harm results.

THE TREATMENT OF ADVANCED CASES.

In hospital practice, owing to the fact that in the greater number of cases admitted the disease has reached the advanced stage, many patients do not receive the first dose before the fifth or sixth day, or even later. In such instances the dose is large, ranging from 20,000 to 50,000 units. This illustrates the

necessity of large doses when treatment is delayed. The fact that the amount of antitoxin which is necessary to save life increases at a rapidly accelerating rate, according to the length of time which elapses between infection and the administration of the serum, has been proved by animal experiments as well as by hospital experience.

In cases demanding immediate relief, the antitoxin should be administered intravenously, with due caution.

PROPHYLACTIC USE OF DIPHTHERIA ANTITOXIC SERUM.

Diphtheria antitoxin is a valuable prophylactic agent, but it must always be remembered that the passive immunity produced by its use is only temporary, lasting probably not more than three weeks. A prophylactic dose of at least 1,000 units may be administered to all other members of the family whereof one member has been attacked by diphtheria. When once a bulb of serum has been opened it is imperative that no portion of the contents be reserved for future use; therefore it is advisable to use the whole at once in one or more cases.

CONCENTRATED DIPHTHERIA ANTITOXIN.

One difficulty in the administration of large doses of diphtheria antitoxin consists in the

inconveniences attending the subcutaneous injection of bulky doses. Since its introduction manufacturers have persisted in attempting to isolate the antitoxin from the serum. The early discovery was made that the antitoxic element in the serum is either a globulin or so intimately associated with the globulin content as to precipitate with it. There are various methods by which this result is attained, all these methods being based on the principle of repeated precipitation. The method now being employed in our laboratory produces a globulin that is free from many of the albuminous substances which cause the undesirable by-effects of serum administration. These proteins which are removed in the process of concentration are largely responsible for the toxic symptoms which sera may produce in susceptible patients.

With Parke, Davis & Co.'s Concentrated Antidiphtheric Serum (Globulin) and Antidiphtheric Globulin (Dry), it is found in practice that rashes and other undesirable symptoms occur less frequently than with untreated serum, and when they do occur they are of a milder type.

TOPICAL AND CONSTITUTIONAL TREATMENT.

Though curative results usually follow the use of antidiphtheric serum alone, still it is well to call to mind the fact that the serum

is not antimicrobic, but only antitoxic, hence the additional advantage of treating the throat antiseptically. For this purpose sprays of hydrogen peroxide solution (P. D. & Co.) may be used freely; also inhalations from boiling water with the addition of fluid benzoin (P. D. & Co.); and if a tendency to hemorrhage be present, the throat and nose may be sprayed with Adrenalin Inhalant (P. D. & Co.). In addition to the use of the serum and local treatment of the throat and nose, proper constitutional treatment should be instituted and the activity of the eliminative functions should be maintained.

ALLERGIC REACTIONS ATTENDING THE ADMINISTRATION OF SERUM.

Undesirable symptoms resulting from a hypersensitive condition of the patient to the injection of foreign protein are sometimes encountered in the use of serum products. In a considerable number of cases the administration of serum is attended with a symptom complex designated "serum sickness," and characterized by rashes (usually urticarial), enlargement of the lymph nodes, edema, painful joints, pyrexia, and albuminuria. The entire chain of symptoms is not present in every case of serum sickness, the only constant manifestation being the skin eruption. In patients who have never before been treated

with serum the symptoms of serum sickness, if they are to appear at all, usually develop eight to twelve days after the injection, while in those who have received previous injections they develop earlier, often within forty-eight hours, and are usually more severe. Serum sickness is an annoying but not a dangerous condition, the symptoms usually disappearing within a few days and leaving the patient none the worse for the attack. It is estimated that 20 per cent. of all cases injected with serum exhibit some of the symptoms of serum sickness. A few cases are on record of profound and even fatal collapse attending the administration of serum. In most of these cases the symptoms have developed within fifteen to twenty minutes after the injection of the serum, and in patients not previously treated with serum. The underlying factor is believed to be a hypersensitiveness to the serum albumin, probably associated with an instability of the vasomotor apparatus. Patients evidencing an overgrowth of the lymphatic tissue are regarded as more likely to develop severe reactions than others.

DESENSITIZATION.

The use of concentrated or globulin antitoxin has reduced the case incidence as well as the severity of serum sickness, and it is now

believed that by proper precaution it is possible to practically eliminate the danger of sudden collapse. Experiments on the lower animals have demonstrated that sensitization to a specific protein can be destroyed—in other words, that the animals can be desensitized by the injection of a very small amount of the protein, so that subsequently large doses of serum or other protein can be given without the production of toxic symptoms. The desensitization of the human subject is therefore suggested as a rational procedure, and has been tried on an extensive scale. Besredka, of the Pasteur Institute in Paris, offers the following method of procedure: "By making serum injections into veins, first a drop, a half-minute later a few, than after a little time some more, and so on, we may safely inject any size of dose of serum without fear, the whole not requiring more than five minutes more time than we give to the same operation when taking no precaution. The increased safety is well worth the extra time." The more common procedure is to inject subcutaneously or intramuscularly a few drops of the serum (0.1 Cc.) and to withhold the balance of the injection for a period of from one-half hour to an hour.

UNUSUAL USES OF ANTIDIPHTHERIC SERUM.

Aside from the specific therapeutic uses of antidiphtheric serum (the prevention and cure of diphtheria), the serum has been successfully employed and highly recommended by many clinicians in various affections, among which are the following: scarlet fever, quinsy, tonsillitis, bronchopneumonia, measles, cancrum oris, tubercular diseases, conjunctival diphtheria, ocular inflammation, exophthalmic goitre, rhinorrhea, asthma, whooping-cough, boils and carbuncles, chronic skin diseases, hemorrhage, hematemesis and hemoptysis, erysipelas and other septic infections. It has been administered in most of these affections, of course, by the injection method; in some cases, however, it has been given by the mouth, and in a few cases per rectum.

It would seem that this specific serum has a very wide therapeutic range, to which the general profession have paid but scant if any notice.

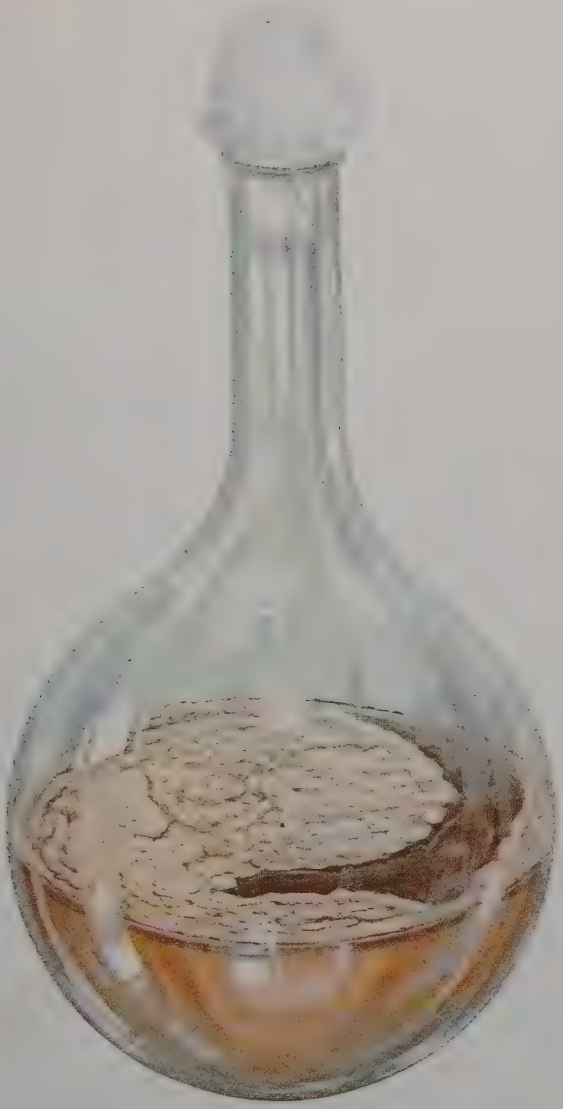
ANTITETANIC SERUM.

Antitetanic serum is obtained from the blood of horses that have been immunized to the toxin of the tetanus bacillus. Some clinicians deny that its results are curative, although there is abundant evidence that its timely administration does *prevent* tetanus. The cause of failure is probably due to the fact

that the serum frequently is not administered until muscular spasms occur, while the rationale of its action depends upon its early administration before the neurotoxic effect occurs. When the symptoms of tetanus have developed the toxin has already invaded the motor nerve cells, forming a union so strong that the antitoxin is powerless to break it up, though it may possibly check the further progress of the disease; whereas, if the antitoxin is given early, the toxin is neutralized before it reaches the motor cells and is thereby rendered harmless.

The numerous reported instances of recovery brought about by the administration of the serum, notwithstanding that convulsions had appeared before the first dose was given, emphasize the desirability of using it even in the late stage of the toxemia.

Therapeutics. As a prophylactic, injections of antitetanic serum should be given in all cases of wounds soiled with garden or street dirt or with dung, also those made by splinters or bullets, and with gunpowder. The procedure is to remove, by curetting, the infected tissue, and cleanse the wound thoroughly with hydrogen peroxide solution (P. D. & Co.); dry and pack with gauze well charged with Antitetanic Dusting Powder (P. D. & Co.), providing free drainage, and prevent premature



Bacillus tuberculosis growing on broth.

Staph. pyogenes aureus, gelatin slant. *Staph. pyogenes citreus; gelatin slant.* *Staph. pyogenes albus; gelatin slant.*

The Gram method is used for the staining of these staphylococci.

closure of the wound in order to avoid anaerobic conditions; and inject immediately 1500 units of Antitetanic Serum in the neighborhood of the wound if that is possible—if not, in the subclavicular region. The prophylactic dose of 1500 units should be repeated once or twice during the succeeding ten days. When tetanus symptoms have appeared, resort should be had to large curative doses of the serum; the dose recommended is from 10,000 to 20,000 units, injected intravenously, repeated every four to six hours until all symptoms of the disease disappear. Cases of successful treatment are reported in which as much as 250,000 units was injected. The serum has also been administered by spinal injection, with results sufficiently favorable to warrant this procedure in very grave cases.

ANTITETANIC GLOBULINS (DRY).

This preparation is very convenient for the use of travelers and expeditions. It is a potent and practically a permanent product, retaining its peculiar properties for years in the unbroken package. It consists of the globulins of Antitetanic Serum, precipitated, purified, and dried so that most of the serum constituents have been eliminated except those bearing the antitoxin.

ANTITETANIC DUSTING POWDER.

This is a mixture of equal parts of dried Antitetanic Serum and Chloretone, for use in the treatment of wounds suspected of being infected.

Antitetanic Serum is supplied in plain bulbs of 1,500 units each, three bulbs in a package; also in syringe containers of 1,500 and 3,000 units, respectively; the concentrated serum (Globulin) in syringe containers of 5,000 units. Antitetanic Globulins (Dry) are supplied in sealed glass bulbs of 1,500 units; and the Antitetanic Dusting Powder in 1-gramme vials.

ANTITUBERCLE SERUM.

This serum is obtained from the blood of horses injected with the water-soluble toxic products of Bacterium tuberculosis. We make no claims as to its therapeutic value. It is made in accordance with the best methods known and is, therefore, one of the most reliable products of the kind on the market. There is no way by which to standardize it.

Antitubercle Serum is supplied in bulbs of 1 Cc., 2 Cc., and 4 Cc., respectively.

ANTIGONOCOCCIC SERUM.

This serum is prepared according to the method of Dr. J. C. Torrey, of the Loomis

Research Laboratory, New York. It is made from the blood of horses which have been inoculated with gradually increasing quantities of bacterial suspensions and endotoxin from the most virulent strains of gonococci obtainable; the process throughout is similar to that employed in the production of antidiphtheric serum.

Therapeutics. This serum is especially valuable in the treatment of chronic conditions arising from primary gonococcic infections of the prostate, epididymis, testicle, bladder and Fallopian tubes; also, those due to the entrance of the micro-organisms into the circulation, as arthritis, iritis, endocarditis, pleuritis, and meningitis. The most satisfactory results of its use have been obtained in gonorrheal arthritis; good results have been reported in cases of epididymitis, prostatitis, and orchitis.

The treatment should commence with 2 Cc., to be repeated every two to four days. If no improvement is noted, 4 or even 6 Cc. may be given every fifth day. The majority of cases require from 30 to 50 Cc. of the serum. The places best suited for injections are the thigh, buttocks, abdomen, or the side of the breast, using in every case aseptic precautions. Other treatment, such as local applications and irrigation, should not be neglected.

ANTIMENINGITIC SERUM.

This serum is obtained from the blood of horses immunized against endotoxin and cultures of a number of strains of Diplococcus intracellularis meningitidis. In addition to the tests employed for determining its potency, rigid bacteriologic and physiologic tests are employed to establish its safety.

Therapeutics. This serum is especially intended for the treatment of cerebrospinal meningitis produced by the Diplococcus intracellularis meningitidis. As much depends on an early diagnosis and administration of the serum, it is quite imperative that when the first lumbar puncture is made for securing the spinal fluid for bacteriological examination the serum should be administered at once; it is not advisable to await the result of microscopic examination. It has been observed clinically that in the presence of the Diplococcus intracellularis meningitidis the spinal fluid is more turbid than in other types of infection.

The dose usually administered to young children is 15 Cc., while for an adult or in malignant cases 30 Cc. (two syringefuls) should be injected at each dose. In severe and fulminant cases a dose of 45 Cc. should be injected if indications to the contrary do not exist. The amount of serum injected should be equal in volume to the amount of spinal

fluid withdrawn. Four daily injections should be given, and in resistant types of the disease it will be found necessary to give six, eight, or even more injections.

With each package is provided a special needle with a stylet. This needle affords a means for both withdrawing the cerebrospinal fluid and injecting the serum. The operator should take special pains to see that the stylet is fitted into place so that the bevel corresponds to that of the needle point before making the lumbar puncture. Rigid asepsis is essential to the successful use of the serum, therefore the same care should be exercised as in a major operation.

The serum is supplied in 15-Cc. syringe containers, two in a package, with the special needle and stylet, and two rubber connections for the needle.

ANTISTREPTOCOCCIC SERUM
(POLYVALENT)

This serum is prepared by immunizing horses with increasing doses of killed bouillon cultures of streptococci representing strains from puerperal fever, erysipelas, scarlet fever, pseudo-diphtheria, endocarditis, and other forms of streptococcus septicemia.

It is believed that antistreptococcic serum is mainly, if not entirely, bacteriolytic.

Therapeutics. Infection with virulent strep-

tococci is not infrequent in injuries and abortions, giving rise to a systemic toxemia. It occurs also in erysipelas, pneumonia, pyemia, scarlet fever, parturition, certain forms of tuberculosis, etc. When the toxemia is but slight an injection of 10 Cc. of antistreptococcic serum every eight to twelve hours may suffice, but in severe cases it is necessary to give from 20 to 40 Cc. every six to eight hours. It has been advised that in severe forms of toxemia no less than 300 Cc. should be given during twenty-four hours (60 to 80 Cc. administered every four hours for twenty-four to thirty hours). It has also been reported that a synergistic action is obtained by injecting strepto. bacterin at the same time with the serum, as the bacterin increases the amount of antibodies in the patient's blood, thereby increasing his resistance to the disease.

The infections in which antistreptococcic serum is indicated are: endocarditis, puerperal sepsis, septicemia, erysipelas, acute tonsillitis, septic pharyngitis, malignant scarlet fever, pneumonia and pleurisy, purpura hemorrhagica, streptococcus sore throat, meningitis, chronic gonorrheal infection, articular rheumatism, and iritis. This serum has been administered both hypodermatically and per rectum in diseases presumably due to streptococcus infection, and in some in which the infective agent was not determined.

Antistreptococcic Serum is supplied in 10-Cc. and 20-Cc. syringe containers, and in 10-Cc. glass bulbs, three bulbs to a package. The dose is 20 Cc. to 80 Cc. every four to six hours until the temperature is reduced and symptoms of toxemia disappear.

METHODS OF ADMINISTRATION OF THE SERA.

Except in the case of Antimeningitic Serum, the hypodermatic injection method is adopted in the majority of cases. This method affords rapid absorption, and the dose is readily and exactly regulated. Aseptic precautions are always observed. The most approved site for the injection is between the scapulæ or under the skin of the abdomen, and the serum is allowed to become absorbed naturally; the swelling over the point of injection readily disappears.

The intravenous injection method is adopted in the more desperate cases, and its use is likely to become more general.

The intraspinal injection method is used in cases of cerebrospinal meningitis, for the Antimeningitic Serum, and Antitetanic Serum has been administered by this method in grave cases with favorable results.

Rectal administration of Antistreptococcic Serum, polyvalent, has shown as favorable results as those obtained by the hypodermatic method.

Section 4.

BACTERIAL VACCINES OR BACTERINS.

The terms "vaccine" and "vaccination" had their origin in Jenner's method of producing immunity to smallpox by means of inoculation with the virus of vaccinia. These terms have now taken on a wider application, and in any case in which inoculation with a killed culture or attenuated virus of a disease is employed to bring about a condition of immunity or resistance to that disease, the terms vaccine and vaccination are applied. The extension of the method naturally resulted in the extension of meaning. Pasteur's production of a protective anthrax vaccine, and later a hydrophobia vaccine, was the beginning of a very rapid advance, until to-day a large number of vaccines are in use for both curative and prophylactic purposes, and in a variety of diseases. Many of these have proved of great value, making possible a degree of success in the treatment of certain bacterial diseases not possible with older methods. These results have given to vaccines an established place in the treatment of germ diseases, and also in their prevention.

In the case of diseases of which the bacterial

origin is known, pure killed cultures of the causal agent are used for the inoculation, and the vaccine is called a bacterial vaccine. Living cultures are seldom made use of; the safest and common method of vaccination is with killed cultures.

Bacterial vaccines are sterilized, standardized suspensions of micro-organisms. They are prepared by washing the films off agar cultures into a 0.9-per-cent saline solution, sterilizing by heating to a temperature just sufficient (55° or 60° C.) to kill the organisms, and diluting with trikresolated normal salt solution until each cubic centimeter contains the number of micro-organisms desired.

The vaccines are subjected to bacteriological tests for purity.

SOURCE OF THE CULTURES.

The micro-organisms used in making bacterial vaccines are either cultivated from the patient's own disease process, in which case the vaccines are called personal or autogenous vaccines; or germs of the same species as those infecting the patient are obtained from previous similar cases, in which case the vaccine is called a stock vaccine.

The advantages of stock vaccines outweigh the advantages of autogenous vaccines. Stock vaccines can be kept on hand and

administered without delay to the patient upon his first visit to the physician, whereas several days are required to prepare autogenous vaccines. Autogenous vaccines may be more efficacious than stock vaccines in some conditions, being more exactly suited to the particular patient; on the other hand, satisfactory results in the great majority of cases follow the use of stock vaccines. However, treatment may well be begun with the stock vaccines and finished, if need be, with autogenous vaccines. Again, autogenous vaccines are not only impractical but impossible in gonorrhea and tuberculosis, owing to difficulties encountered in growing the germs, and in staphylococcus infections are usually unnecessary owing to the fact that stock vaccines do quite as well in most cases. Finally, autogenous vaccines can be prepared only by a well-trained laboratory worker, while stock vaccines are ready for instant use by the general practitioner.

THERAPEUTIC ACTION OF BACTERIAL VACCINES.

When bacterial vaccines are injected into human beings they have an effect similar to that produced on the horse by the injection of toxins or killed cultures; they produce *active* immunity. In other words, the injection of a dose of a bacterial vaccine stimulates the patient's body to produce an additional

supply of antibodies and thus enables him to resist the disease.

In the use of serums the antibodies are supplied to the patient; in the use of bacterial vaccines he develops his own antibodies. Serums confer *passive* immunity, vaccines *active* immunity.

As bacterial vaccines are used in accordance with the principles elucidated by Sir A. E. Wright, of London, England, it is only fitting that we give here his enunciation of the opsonic index theory.

THE OPSONIC INDEX.

The opsonic index is the ratio between the average number of bacteria found within 50 to 100 leucocytes in a suspension containing bacteria, blood corpuscles and the patient's serum, and the average found in the same number of leucocytes in a corresponding suspension containing normal serum, the latter being taken as the standard.

In a large number of infections, protective substances (opsonins) exist in the blood serum. The opsonins are thermolabile; the serum containing them is inactivated (that is, deprived of its opsonins) if heated to 56° C. for a few minutes. The opsonins act upon the bacteria, so that the latter can subsequently be ingested by the leucocytes. When the different blood specimens are compared, the variable factor

is the serum and not the leucocytes. The specific opsonin is consumed when bacteria are added to a serum containing it, for if the bacteria are then removed and the serum used with a second portion of the same suspension it is found to be inactive. The opsonins become combined with or at least absorbed by the bacteria, so that bacteria removed after treatment and placed in an inactivated serum are freely taken up by leucocytes added to the serum. By careful vaccination with small measured quantities of dead cultures of various pathogenic micro-organisms it is possible to increase markedly the opsonizing power of the serum of an individual. Regarding phagocytosis as the main process by which bacteria are destroyed within the organism, and the opsonins as the means whereby the bacteria are prepared for ingestion, Wright concluded that the relative amount of opsonins in a given serum affords an indication of the defensive power of the individual.

The technique of taking the opsonic index may be described in the following stages:

1. COLLECTING THE BLOOD TO BE TESTED.

By pricking the finger or the lobule of the ear the blood is obtained. It is drawn into a Wright capsule or a Widal tube, and the container is sealed with wax. One capsule of known normal blood is drawn. The capsules

are numbered for identification, and left until the serum separates, or it may be centrifugalized to save time.

2. PREPARING THE BLOOD-CORPUSCLES.

A few drops of blood from the finger are run into a test tube which contains sodium citrate solution, 1½ per cent., until the proportion is about two-thirds citrate solution and one-third blood. The contents are then gently mixed and centrifugalized for three minutes. The fluid is pipetted off, and normal salt solution is added to the corpuscles. The centrifugalizing is repeated, and the fluid again pipetted off, leaving only the layer of red and white corpuscles in the tube; with a pipette these corpuscles are gently mixed, and are now ready for use.

3. PREPARING THE SUSPENSION OF BACTERIA.

The organisms, grown on agar, are removed, and suspended in salt solution. If necessary to break up clumps the culture should be shaken. The suspension is centrifugalized, pipetted off into a fresh tube, and thoroughly mixed. It should then be examined as an ordinary smear preparation to be certain of its freedom from clumps.

The salt solution used in the suspension is 0.85 per cent. saline, except in the case of tubercle bacilli and the non-gram-staining cocci, for which a 1.5 per cent. saline solution is used.

4. COMBINING FOR THE TEST.

With a pipette having a long stem, equal quantities of the washed blood-corpuscles, the bacterial suspension, and the serum to be tested are taken up, driven out on to a slide to be thoroughly mixed, and redrawn into the pipette; the end of the pipette is then sealed in a flame, care being taken to keep the suspension away from the heated end. The pipette is then incubated at 37° C.; in the case of typhoid and other coliform organisms 8 to 10 minutes is quite sufficient, and for other organisms 15 to 20 minutes.

5. PREPARING THE FILM.

On removing the pipette from the incubator, the sealed end is broken off, and some of the suspension expressed upon a slide and thoroughly stirred. A drop of this mixture is then placed on another slide, and spreading it with the slightly concave edge of an ordinary slide a film is made in which all the white corpuscles are swept to one end, where they are fixed and stained with the appropriate staining fluid.

6. COUNTING.

The micro-organisms in 100 polymorphonuclear leucocytes are counted. The average number of bacteria per leucocyte is the phagocytic index. The consistency of the suspension of bacteria should be such as to

facilitate a ready enumeration of the microorganisms in each leucocyte.

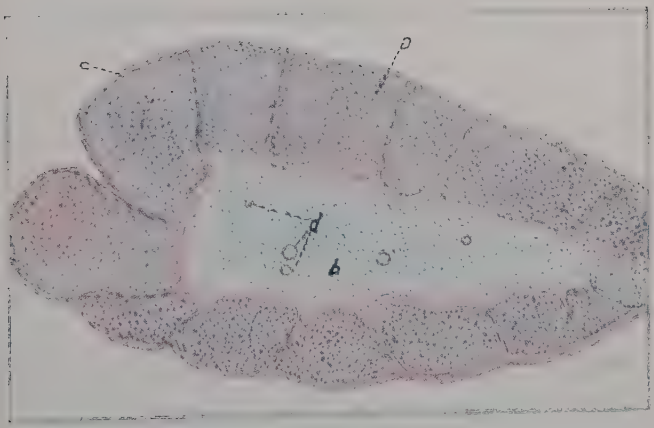
The quotient of the number of organisms in 100 leucocytes from the patient's serum, divided by the number in 100 leucocytes from the normal serum, is the opsonic index.

The opsonic index may be used as the controlling factor in the administration of vaccines.

THE NEGATIVE AND POSITIVE PHASES.

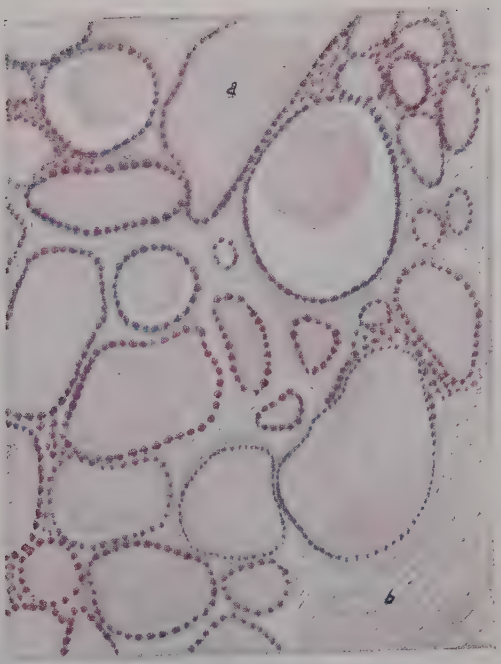
Vaccines are used to aid the natural development of immunity, and the progress of this immunizing process may be gauged with a fair degree of accuracy by taking the opsonic index from time to time, the vaccine being regularly administered, both as to time and dosage, in accordance with the index. The injection of vaccine is followed by a slight fall of the opsonic index. This is the "negative phase," which may continue from one to several days, and is succeeded by a rise in the opsonic index, indicating a "positive phase," during which the specific opsonin is produced in excess, and in consequence resistance is increased.

An average dose of vaccine given at a stated time will produce a short negative phase, followed by a prolonged positive phase. If the dose given be too large, the negative phase is prolonged. No additional injection should be given during the negative phase, as this pro-

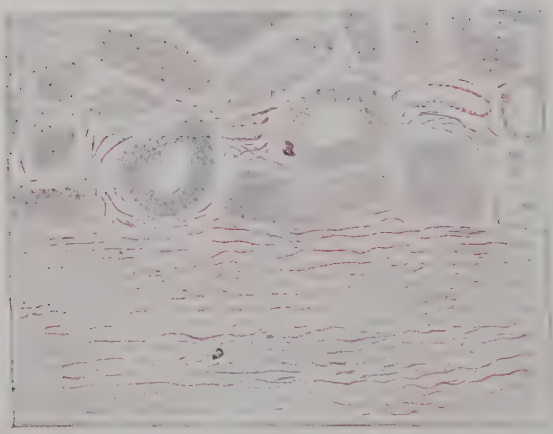


Thymus Gland. a, cortex; b, medulla; c, capsule; d, blood-vessels.

Liter's Glands in gonorrheal urethritis - showing gonococci in and about pus cells. a, gland crypt; b, gonococci; c, white cells.



Simple Goitre, showing over-abundance of colloid material-a; b, connective tissue.



Pituitary body through junction of anterior and posterior lobes.
a, anterior secreting portion and blood-vessels; b, posterior nervous portion-multipolar cells.

cedure causes a still further fall in the index, a condition termed the "cumulative negative phase." A series of injections of proper size and at stated intervals causes a very great rise in the opsonic index, termed the "cumulative positive phase." By this method of procedure Wright obtained excellent results and thereby gave a great impetus to the practice and study of vaccine therapy.

INDICATIONS FOR VACCINES.

The diseases in which bacterial vaccines have proved most valuable are those described as chronic localized infections, and in recalling the process of natural immunity or recovery we are reminded why this should be so.

According to Wright, the natural cure of any bacterial disease consists in a series of auto-inoculations and immunizing responses, the infectious agent being derived from the focus of infection in the body; and the effect of each immunizing response is to increase further the resistance of the body, until finally immunity is complete and the disease cured.

In the mass of microbic infections the normal mechanism of immunity is fully capable of dealing with the invading organism, but in a certain percentage of cases this result is not produced; the immunizing mechanism fails, either from inherent weakness or from the virulent nature of the infection, and this is

attended by an excessive outpouring of bacteria or their toxins from the focus of infection in the body. In the case of chronic localized infections the amount of bacteria or their products which is poured out is small; the immunizing response is likewise inconsiderable, and therefore inadequate to overcome the infection; hence the lesion tends to persist. Thus we are led to assume, and thus clinical results have demonstrated, that it is in this latter class of cases that the benefits of inoculation with vaccines are most marked.

The fact must not be lost sight of that many cases are quite unsuitable for treatment by means of vaccines. In some cases routine methods may be adopted. In other cases the effect of each dose of vaccine must be carefully noted, and the treatment must proceed with careful observation. In other words, carefully select the cases for treatment with the vaccines, and the results will be commensurate with the care bestowed upon their selection.

HOW SERUMS AND VACCINES PREVENT DISEASE.

They act precisely as they do when used for their therapeutic effect. The injection of 1,500 units of antitetanic serum supplies sufficient antitoxin to prevent the development of tetanus after infection. It confers *passive* immunity. The injection should be made immediately after receipt of the injury, or as soon

thereafter as possible. Its efficiency as a prophylactic has been demonstrated many times. The injection of a dose of typhoid vaccine stimulates the elaboration in the patient's body of sufficient antibodies to prevent the development of typhoid fever. It confers *active* immunity.

CONFUSION OF TERMS.

Some confusion as to the use of the names of these various products appears to exist in the minds of students and others. This is very readily cleared up by remembering that the serums contain *anti*bodies; they are therefore classed as *anti*diphtheric serum, *anti*tetanic serum, *anti*gonococcic serum, *anti*streptococcic serum, etc. The bacterial vaccines do not contain antibodies. They are classed as streptococcus vaccine, gonococcus vaccine, staphylococcus vaccine, colon vaccine, etc.

WHEN SHOULD SERUMS BE USED, AND WHEN BACTERIAL VACCINES?

When the condition of the patient is such that he cannot produce his own antibodies it is necessary to supply them by an injection of serum. Thus serums give the best results in acute general infections.

At the very outset infectious processes are usually localized, and in such cases the prompt use of a suitable bacterial vaccine is indicated.

Thus it will be observed that the extent of the infection is a guide to the proper selection of the serum or vaccine to be employed. Stated in another way, bacterial vaccines are most useful in localized and semi-localized infections, and serums are indicated in general infections.

Example.—Dr. Geo. F. Seaborn (*New York State Journal of Medicine*, April, 1911) illustrates this point very aptly as follows: "In the early stage of puerperal sepsis, before general infection has taken place, we may expect beneficial results from a bacterial vaccine; but when the infection has been allowed to run its course unchecked until it becomes more or less general, antistreptococcic serum, if the infection is due to the streptococcus, should prove of greater value than streptococcus vaccine."

Of the bacterial vaccines which have now a recognized place in vaccine therapy, Parke, Davis & Company supply Acne Vaccine, Acne Vaccine Combined, Catarrhal Vaccine Combined, Colon Vaccine, Combined Bacterial Vaccine (Van Cott), Furunculosis Vaccine, Gonococcus Vaccine, Gonorrheal Vaccine Combined, Meningococcus Vaccine (prophylactic), Urethritis Vaccine Combined, Pertussis Vaccine, Pertussis Vaccine Combined, Pneumococcus Vaccine, Pneumonia Vaccine Combined, Pyorrhea Alveolaris Vaccine Com-

bined, Staphylococcus Vaccines (three varieties and a combination of the three), Streptococcus Vaccine, Typhoid Vaccine (prophylactic), Typhoid-paratyphoid Vaccine (prophylactic), Vaccine Virus (smallpox), and Pasteur Antirabic Vaccine (Cumming).

ACNE VACCINE

(ACNE BACTERIN).

Prepared from cultures of Bacterium acne vulgaris grown under anaerobic conditions.

Therapeutics. Indicated in all forms of acne vulgaris. Clinical results show that it gives almost as satisfactory results in the pustular as in the indurated type of acne, thus indicating that the Bacterium acne vulgaris is the exciting cause and that the staphylococcic infection is negligible.

Dose. Five to ten millions is a satisfactory initial dose, and subsequent injections should be given every four to seven days, the dose being gradually increased by increments of five to ten millions up to 100 millions, if necessary.

Acne Vaccine is supplied in rubber-stoppered bulbs of 20 million and 100 million, respectively, four bulbs in a package; also in graduated syringes of 20 million and 100 million, respectively, either a single syringe in a package, or packages containing four syringes, and in bulk packages of 5 Cc. and 20 Cc.

ACNE VACCINE COMBINED

(ACNE BACTERIN COMBINED).

Each cubic centimeter contains killed cultures of Bacterium acne, Diplococcus acne, Staphylococcus albus, aureus, and citreus, of each 100 millions—total, 500 millions.

Therapeutics. Indicated in acne of the mixed type—indurated and pustular—and in cases that do not respond satisfactorily to treatment with Acne Vaccine or Staphylococcus Vaccine; also in the treatment of boils, carbuncles, acne rosacea, sycosis, eczema, chronic ulcers, and inflammatory affections of the skin and underlying cellular tissue.

Dose. Begin with not more than 50 millions and increase by 50 to 125 millions, as indicated, at intervals of four to seven days. It may be necessary in some cases to give the entire contents of a bulb or syringe at a single dose.

Acne Vaccine Combined is supplied in rubber-stoppered bulbs of 500 millions, four bulbs in a package; also in graduated syringes of 500 millions, in packages of one and four, and in bulk packages of 5 Cc. and 20 Cc.

CATARRHAL VACCINE COMBINED

(CATARRHAL BACTERIN COMBINED).

A killed culture of Micrococcus catarrhalis, 50 millions; Diplococcus pneumoniæ (Fraenkel), 50 millions; Bacillus pneumoniæ

(Friedlander), 50 millions; Streptococcus pyogenes, 50 millions; Bacillus septus (diphtheroids), 100 millions; Staphylococcus albus, 100 millions; and Staphylococcus aureus, 100 millions—total, 500 million bacteria in each Cc.

Catarrhal Vaccine Combined is used in the treatment of acute and chronic catarrhal conditions of the throat and nose, such as rhinitis, pharyngitis, laryngitis, bronchitis, etc. Initial dose, 250 millions.

Catarrhal Vaccine Combined is supplied in rubber-stoppered bulbs of 1 Cc., four in a package; and in 1-Cc. graduated syringes in packages of one and four; also in bulk packages of 5 Cc. and 20 Cc.

COLON VACCINE

(COLON BACTERIN).

A killed culture of Bacillus coli communis in sterile solution.

Therapeutics. Employed in the treatment of colon infections of the genito-urinary and biliary tracts; *e.g.*, cystitis, pyelitis, cholecystitis, rectal abscess, fistula in ano, prostatitis, pyosalpinx, ulceration of the colon, acute jaundice, and vulvovaginitis of children.

Dose. The initial dose is 50 millions, and this may be increased to 100 millions, in accordance with the usual rule.

Colon Vaccine is supplied in rubber-stop-

pered bulbs of 200 millions and 500 millions, respectively, four bulbs in a package; also in graduated syringes of 200 millions and 500 millions, respectively, in packages of one and four, and in bulk packages of 5 Cc. and 20 Cc.

COMBINED BACTERIAL VACCINE (VAN COTT).

Each cubic centimeter contains killed cultures of Streptococcus pyogenes, 50 millions; Staphylococcus aureus, albus, and citreus, 500 millions; Bacillus coli communis, 100 millions; and Diplococcus pneumoniæ, 100 millions—total, 750 millions.

Therapeutics. This vaccine has been used with marked success in erysipelas, puerperal sepsis, phlegmon, mastoiditis, malignant endocarditis, acute tonsillitis, and in a variety of suppurative infections the exact bacterial nature of which could not be diagnosticated.

Dose. The initial dose is about 400 millions, and the range of dose may in severe puerperal sepsis reach 1500 millions. In ordinary cases the dose may be repeated every four days, if necessary.

Combined Bacterial Vaccine (Van Cott) is supplied in rubber-stoppered bulbs of 750 millions, four bulbs in a package; in syringe containers of 750 million, in packages of one and four; and in bulk packages of 5 Cc. and 20 Cc.

FURUNCULOSIS VACCINE

(FURUNCULOSIS BACTERIN).

Each cubic centimeter contains killed cultures of Staphylococcus aureus obtained from the furuncular lesions (boils or other circumscribed abscesses) of a considerable number of cases.

Therapeutics. This vaccine is indicated in the treatment of infections with the Staphylococcus pyogenes aureus, and is of specific efficiency in the treatment of boils, carbuncles, impetigo contagiosa, pustular acne, and sycosis staphylogenes.

Dose. The initial dose should not exceed 100 to 150 millions; the second dose, within four days, is 200 to 250 millions; should a third dose be necessary 300 to 400 millions may be administered four days after the second dose. Subsequent dosage must be governed, as regards both intervals and amounts, by the clinical indications.

Furunculosis Vaccine is supplied in rubber-stoppered bulbs and in graduated syringes of 400 millions, the bulbs in packages of four, and the syringes in packages of one and four; also in bulk packages of 5 Cc. and 20 Cc.

GONOCOCCUS VACCINE

(GONOCOCCUS BACTERIN).

Killed cultures of the Micrococcus gonorrheæ, each cubic centimeter containing 20

millions, 100 millions or 500 millions, as specified.

Therapeutics. In the treatment of gonorrhea and its complications, including gleet, epididymitis, gonorrheal ophthalmia, prostatitis, arthritis, seminal vesiculitis, vulvovaginitis, and as a preventive and curative agent in pyosalpinx. In acute urethritis, results are uncertain.

Dose. The initial dose is 5 to 20 millions. In general the dose should be gradually increased up to 100 millions or even as high as 500 millions. A slight local reaction may follow the initial dose. Constitutional disturbances are rare. The number of doses varies from one to eight; the intervals between doses are three to six days.

Gonococcus Vaccine is supplied in rubber-stoppered bulbs of 20 millions, and in bulbs and graduated syringes of 100 millions and 500 millions, the bulbs in packages of four and the syringes in packages of one and four; also in bulk packages of 5 Cc. and 20 Cc.

GONORRHEAL VACCINE COMBINED

(GONORRHEAL BACTERIN COMBINED).

Each cubic centimeter contains killed cultures of Micrococcus gonorrheæ, 500 millions; combined Staphylococcus albus, aureus, and citreus, 400 millions—total, 900 milllions.

Therapeutics. In the treatment of gonor-

rheal infections with staphylococcic complications; these cases include chronic posterior urethritis, prostatitis, epididymitis, pyosalpinx, salpingitis, etc.

Dose. As a general rule 100 to 250 millions is regarded a safe initial dose, to be followed, if necessary, at intervals of five or six days by gradually increasing doses, the size of the dose and intervals between them to be governed by the reaction following the last previous dose. Such symptoms of disturbance as headache, malaise, etc., should be avoided if possible.

Gonorrheal Vaccine Combined is supplied in rubber-stoppered bulbs and in graduated syringes, the bulbs in packages of four, and the syringes in packages of one and four; also in bulk packages of 5 Cc. and 20 Cc.

MENINGOCOCCUS VACCINE (PROPHYLACTIC).

Killed cultures of Diplococcus intracellularis meningitidis, 500 millions and 1000 millions in each cubic centimeter.

Uses. This vaccine is for immunization and for use in the treatment of meningococcus "carriers," for checking the spread of epidemic cerebrospinal meningitis.

Dose. In using Meningococcus Vaccine it is important that the treatment be energetic, therefore three injections, the first of 500 millions, and the second and third of 1000 mil-

lions each, should be given at intervals of seven days. This constitutes the usual treatment. In the treatment of meningococcus "carriers" these large doses are neither necessary nor advisable, as a too severe reaction would lower the resistance of the patient and possibly lead to infection; therefore the initial dose should be 100 millions, and the subsequent doses, at intervals of five to seven days, increased by 50 to 100 millions at each injection.

Meningococcus Vaccine is supplied in four packages—containing respectively three bulbs, thirty bulbs, one syringe, and three syringes. In the three-bulb package one bulb contains 500 millions and the other two 1000 millions each; the same is true of the three-syringe package; in the 30-bulb or "hospital" package 10 bulbs contain 500 millions each and twenty 1000 millions each; while the single syringe package contains 2½ cubic centimeters, each cubic centimeter representing 1000 millions.

PASTEUR ANTIRABIC VACCINE (CUMMING).

An improved method of preparing Pasteur Antirabic Vaccine has been devised and perfected by Dr. James G. Cumming, superintendent of the Pasteur Institute, University of Michigan. It consists in dialyzing the standard suspension of rabic brain tissue

against running distilled water until the infectivity of the virus is destroyed. An intracranial injection of such a suspension does not produce rabies, as the injection of an undialyzed suspension of a 7-day desiccated rabic cord may. In the prophylactic treatment of patients bitten by a rabid animal, subcutaneous injections of the dialyzed suspension (Pasteur Antirabic Vaccine, Cumming) confer the highest degree of immunity. A series of twelve daily injections of the Pasteur Antirabic Vaccine (Cumming) produces the same degree of immunity as that obtained by the intensive form of the unmodified Pasteur treatment, which consists of twenty-one daily injections. By increasing the number of injections from twelve to twenty-one the immunity is increased proportionately. Not only does one obtain a higher degree of protection by this method, but the immunity is produced at an earlier stage in the course of the treatment than by the other methods. This fact is of especial importance not only in the treatment of severe bites, particularly those of the face, but also in those cases which do not report for treatment earlier than two weeks after having been bitten.

Over five hundred persons bitten by rabid animals have been treated with the Pasteur Antirabic Vaccine (Cumming), P. D. & Co.,

and in no case has hydrophobia developed, nor have any untoward symptoms resulted.

This product is finished in packages of seven 2-Cc. syringe containers, each syringe completely equipped with needle, etc. A full treatment consists of twenty-one doses of 2 Cc. each, or three packages as above described. On receipt of an order we will supply one package of seven syringes immediately, and the remaining two packages at intervals of six days, the material being kept in the meantime in our ice chest to avoid the deterioration that might follow its storage under ordinary room conditions.

Important.—This vaccine is carried in stock in our principal branches in addition to the Detroit laboratory. It may be ordered by wire directly from the nearest branch or from the home office.

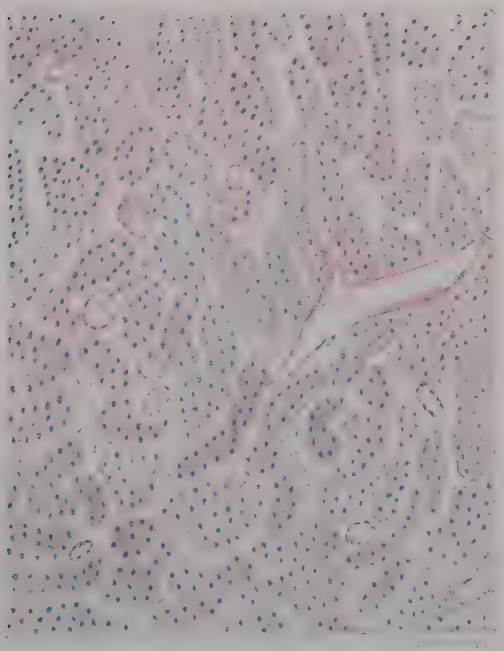
Write us for literature on "Rabies and its Treatment by the General Practitioner."

PERTUSSIS VACCINE

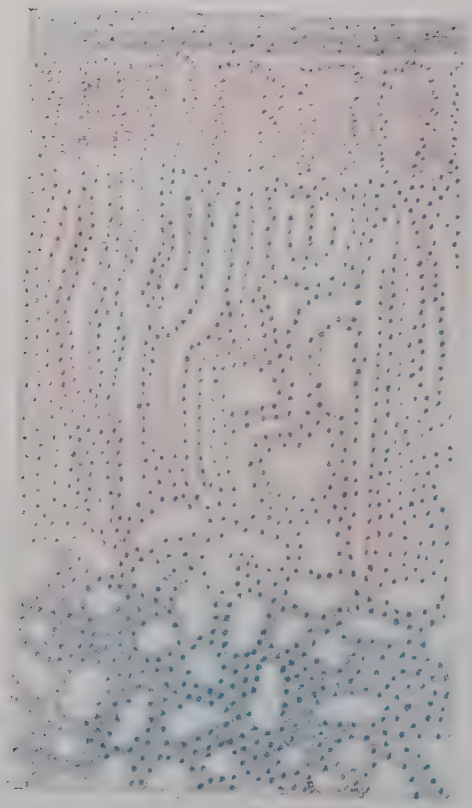
(PERTUSSIS BACTERIN).

Killed cultures of the Bacterium pertussis (Bordet); each cubic centimeter contains 100 millions.

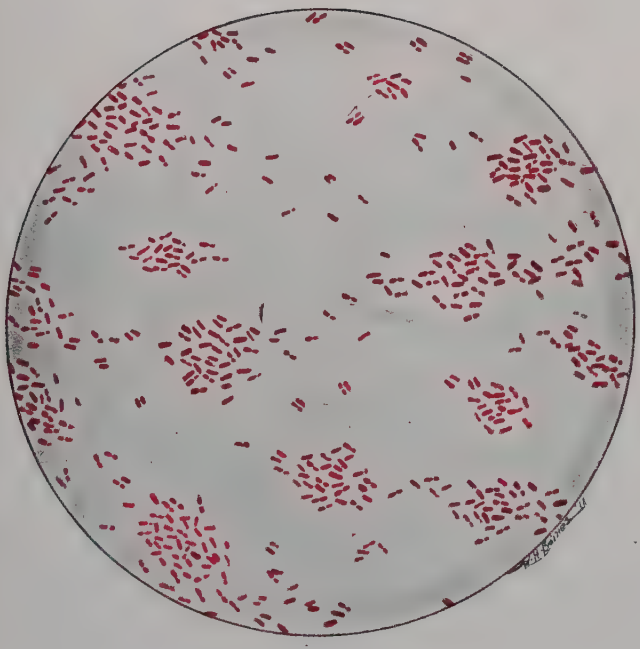
Therapeutics. Indicated in the treatment of whooping-cough and to some extent as a prophylactic; also early in suspected cases. As a prophylactic its value has not been clin-



Exophthalmic Goitre. Increased secreting substance plus dilatation of blood-vessels.



Adrenal, showing: a, capsule; b, zona glomerulosa, c, zona fasiculata, d, zona reticularis



Bacillus coli communis. x 1000.
Drawing from cover-slip preparation.

Bacterium diphtheriæ. x 1000.

ically proved, but during epidemics of pertussis its use is advantageous.

Dose. The initial dose should be 50 millions, and subsequent doses should be given at intervals of three to five days. The clinical symptoms prove the best guide both as to the size of the dose and the frequency of its repetition. The dose may be increased by 20 to 40 millions at a time.

Pertussis Vaccine is supplied in rubber-stoppered bulbs and in graduated syringes, the bulbs in packages of four, and the syringes in packages of one and four; also in bulk packages of 5 Cc and 20 Cc.

PERTUSSIS VACCINE COMBINED

(PERTUSSIS BACTERIN COMBINED).

A killed culture of: Bacterium pertussis of Bordet, 50 millions; Staphylococcus aureus, 20 millions; Streptococcus pyogenes, 10 millions; Micrococcus catarrhalis, 20 millions; Bacterium influenzæ, 20 millions; total, 120 millions in each bulb or syringe, sterile and ready for use.

Pertussis Vaccine (Combined) is indicated in the treatment of all stages of whooping cough (pertussis), but is especially valuable in cases which have persisted for some time, such infections being almost invariably of the mixed type. The vaccine markedly shortens the course of the disease in most cases of

whooping-cough. It decreases both the frequency and severity of the paroxysms, and minimizes the danger of complications, especially the pneumonic involvements. The vaccine is absolutely harmless. Best results are obtained by means of fairly large doses.

Dose. An initial dose of 60 million bacteria (0.5 Cc.) may be employed. Subsequent injections should be given at intervals of from three to five days, the dose being increased at each administration, unless there are indications to the contrary. The production of a marked reaction, either local or constitutional, may be considered a contraindication to an increase in dosage. In the absence of contraindications, with each successive injection the dose should be increased over the preceding from 12 to 24 millions (0.1 to 0.2 Cc.) It is rarely necessary to exceed a dosage of 120 millions.

Pertussis Vaccine Combined is supplied in rubber-stoppered bulbs and in graduated syringes, the bulbs in packages of four, and the syringes in packages of one and four; also in bulk packages of 5 Cc. and 20 Cc.

PNEUMOCOCCUS VACCINE

(PNEUMOCOCCUS BACTERIN).

Killed cultures of the Diplococcus pneumoniæ, supplied in two strengths, one containing

200 million bacteria per Cc., the other 500 million bacteria per Cc.

Therapeutics. Pneumonia Vaccine is indicated in the treatment of lobar pneumonia, and other infections caused by the pneumococcus, including some cases of broncho-pneumonia and localized infections such as ulcus serpens corneæ and otitis media. The Pneumococcus Vaccine is also used as a prophylactic during the season when pneumonia is particularly prevalent and among those individuals who are most exposed to infection. Wright (*Lancet*, January 10, 1914, p. 87) has shown that two or three injections of sterilized cultures of the Diplococcus pneumoniæ in doses from 250 to 1000 millions, given at weekly intervals, produce a considerable degree of immunity to pneumonic infection. Immunity can be depended upon for a period of two to three months.

Dose. For prophylactic treatment, three doses are given at weekly intervals—first, 250 millions; second, 500 millions; third, 1000 millions. For therapeutic purposes the vaccine has been used in doses ranging from two or three millions up to 1000 millions. The best results seem to have followed the administration of large doses early in the course of the disease. Wright did not find that cases treated with small doses (2½ to 50 millions) did any better than those treated by the ordinary

methods, but the prompt use of large doses (250 to 1000 millions) reduced very markedly the mortality. In view of the exhaustive work which he has carried out and the value to be attached to his results, it is suggested that a dose of not less than 200 millions be employed. A dose of 500 millions can probably be given safely to the average case. After an interval of three days a second injection should be given, increasing the dose unless an unusually sharp reaction follows the administration in the first instance. It is believed that a dose of 1000 millions should never be exceeded. The contents of more than one bulb or syringe may be injected when doses larger than 500 millions are desired; or the bulk packages of 5 Cc. or 20 Cc. may be used, each cubic centimeter containing 200 or 500 million bacteria, as specified.

Pneumococcus Vaccine (Pneumococcus Bacterin) is supplied in single syringe containers of 200 and 500 millions each, in packages of four syringes, in packages of four 1-Cc. bulbs, in 5-Cc. vials, and in 20-Cc. vials.

PNEUMONIA VACCINE COMBINED

(PNEUMONIA BACTERIN COMBINED).

This product consists of killed cultures of Diplococcus pneumoniæ, Bacterium pneumoniæ (Friedlander) and Streptococcus pyogenes.

It is supplied in two strengths, 200 million and 1000 million bacteria per Cc., respectively.

Therapeutics. Pneumonia Vaccine Combined is indicated in the treatment of all stages of pneumonia, but is especially valuable in infections of the mixed type.

Dose. The initial dose of Pneumonia Vaccine Combined should be 100 millions; subsequent injections should be given at intervals of three days, the dose being increased at each administration, unless there are indications to the contrary. The production of a marked reaction, either local or constitutional, may be considered a contraindication to an increase in dosage. With each subsequent injection the dose should be increased over the preceding by from 50 to 100 millions.

Pneumonia Vaccine Combined is supplied in rubber-stoppered bulbs of 200 millions and 1000 millions, respectively, four bulbs in a package; in 1-Cc. graduated syringe containers, one and four in a package; and in bulk packages of 5 Cc. and 20 Cc.

PYORRHEA ALVEOLARIS VACCINE COMBINED (HARRIS)

(PYORRHEA BACTERIN).

This preparation contains in each cubic centimeter Streptococcus pyogenes, 40 millions; Staphylococcus pyogenes albus, 200

millions; and Diplococcus pneumoniæ, 40 millions—the cultures being made from material obtained from pyorrhea cases.

Therapeutics. Pyorrhea Alveolaris Vaccine Combined is used in the treatment of purulent inflammations of the dental periosteum.

The vaccine is administered subcutaneously in the usual manner, with strict aseptic precautions. The initial dose should be 140 million bacteria (0.5 Cc.). Subsequent injections may be given at intervals of three to five days. Unless there are indications to the contrary, it is advisable to increase the dose by 28 millions (0.1 Cc.) at each injection until a maximum dose of 280 millions (1 Cc.) has been reached. In obstinate cases it may be necessary to give repeated injections of the maximum dose before definite clinical results are obtained.

To secure the best results, it is imperative that the use of the vaccine be combined with the proper surgical procedures. If this important phase of the work be overlooked the results of the use of the vaccine may be disappointing.

Pyorrhea Alveolaris Vaccine Combined is supplied in 1-Cc. rubber-stoppered bulbs and 1-Cc. graduated syringes, the former in packages of four, the latter in packages of one and four; also in bulk packages of 5 Cc. and 20 Cc.

STAPHYLOCOCCUS VACCINES

(STAPHYLOCOCCUS BACTERINS).

These vaccines are killed cultures of staphylococci, and are four in number: Staphylococcus Albus, Staphylococcus Aureus, Staphylococcus Citreus, and Staphylococcus Combined (albus, aureus, and citreus).

Therapeutics. These vaccines are used in the treatment of suppurating acne, furunculosis, carbuncle, sycosis, osteomyelitis, psoas abscess, infected fistulæ, otitis media, suppurating glands, eczema, septic infections, cystitis, ulcerative endocarditis, and mixed infections.

Dose. Clinical observation of the use of these vaccines would indicate that a satisfactory initial dose ranges from 50 millions to 200 millions. A satisfactory routine is to inject 100 to 125 millions, and at the expiration of four or five days to administer double the amount of the initial dose. In like manner gradually increase the subsequent doses at intervals of five days. When an exact bacteriological diagnosis can be made in any given case of staphylococcic infection the corresponding vaccine should, of course, be used; otherwise the combined vaccine.

Each of the four several varieties of Staphylococcus Vaccine is supplied in rubber-stoppered bulbs and in graduated syringes containing 400 millions and 1000 millions respec-

tively, the bulbs in packages of four and the syringes in packages of one and four; also in bulk packages of 5 Cc. and 20 Cc.

STREPTOCOCCUS VACCINE

(STREPTOCOCCUS BACTERIN).

Killed cultures of the Streptococcus pyogenes, in two dilutions.

Therapeutics. This vaccine is prepared for the treatment of localized forms of infection the causative agent of which is the Streptococcus pyogenes. It is indicated in erysipelas, puerperal sepsis, cellulitis, phlegmon, septic endocarditis, lymphangitis, and in certain mixed infections, especially of tuberculous sinuses and lupus vulgaris.

Dose. The initial dose is 20 to 40 millions, to be gradually increased and as frequently injected as the symptoms of the case indicate and the patient's condition warrants.

Streptococcus Vaccine is supplied in rubber-stoppered bulbs and in graduated syringes of 40 millions and 200 millions, the bulbs in packages of four, the syringes in packages of one and four; also in bulk packages of 5 Cc. and 20 Cc.

TYPHOID VACCINE, PROPHYLACTIC

(TYPHOID BACTERIN).

Killed cultures of the Bacillus typhosus, for preventive inoculation.

Uses. Typhoid vaccine is now in general

use as a prophylactic against typhoid fever. As a protective agent it has been proved to be of great value. The Medical Department of the United States Army was the first to advocate the administration and collect tabulated clinical results from the use of this vaccine. All officers and enlisted men in the United States Army and Navy under 45 years of age are immunized against typhoid fever. The like procedure is being carried out in most of the armies of the world, and this same method is strongly advised in civil practice.

Dose. The first dose is 500 millions, followed in ten days by the second dose, of 1000 millions, and after another ten days by the third dose, of 1000 millions, which completes the treatment for immunization.

TYPHOID VACCINE IN JUVENILE CASES.

In regard to the dose for children, Major Russell (*Journal of the American Medical Association*, Aug. 10, 1913) says: "We vaccinate a great many children; the dose is determined by the weight of the child. The dose for an adult is based on an average of 150 pounds; if a child weighs 50 pounds we give one-third of the adult dose; if the fraction does not come out conveniently, we increase rather than diminish the dose. Children do not react so strongly as adults; it seems to be a rule that the younger the child the less the reaction."

As typhoid fever is a disease that is rare before the age of puberty, it would seem unwise to vaccinate in early childhood; but in children nearing the age of puberty, and who are exposed to infection, vaccination is advisable, particularly since the prophylaxis is supposed to continue for a period of three years or more.

The contraindications are: any departure from the normal health of the patient, especially when fever is present, and in women the presence or near approach of the menses.

THE CURATIVE EFFECT.

Current literature is recording clinical results of typhoid vaccine as a curative agent, and these results tend to show that vaccine therapy in proper hands lowers the death rate, diminishes relapses, and lessens complications. The dosage of typhoid vaccine as a curative agent ranges from 10 millions for the initial dose to 800 millions, a maximum dose, the average being 200 millions. The number of doses ranges from one to eleven, at intervals of twenty-four hours to seven days—average, three days.

Typhoid Vaccine is supplied in four packages —containing respectively three bulbs, thirty bulbs, one syringe, and three syringes. In the three-bulb and three-syringe packages one of the bulbs or syringes contains 500 millions,

and the other two 1000 millions each; in the 30-bulb or "hospital" package, ten of the bulbs contain 500 millions each, and twenty 1000 millions each; while the single syringe package contains 2½ cubic centimeters, each cubic centimeter representing 1000 millions. The bulbs are all rubber-stoppered, and the syringes graduated--so the vaccine can be administered fractionally to children from either bulbs or syringes, or in successive doses to adults from the 2½-Cc. syringe.

TYPHOID-PARATYPHOID VACCINE, PROPHYLACTIC

(TYPHOID-PARATYPHOID BACTERIN).

Killed cultures of the Bacillus typhosus and the Bacillus paratyphosus A and B in sterile suspension, for the prevention of typhoid and paratyphoid infections.

Of our two Typhoid-Paratyphoid vaccines, one contains 4 parts of B. typhosus to 2 parts of B. paratyphosus "A" and "B;" the other equal parts of the Eberth bacillus and the paratyphoid germs. The former is supplied in doses of 500 and 1000 millions, the latter in doses of 1000 and 2000 millions, the bulk of the doses being the same in both cases.

Uses. Frequently cases diagnosed typhoid fever are due to the paratyphoid bacilli. In epidemics or exposures in which there is doubt

of the presence exclusively of the Bacillus typhosus, this should be the vaccine preferred in immunization.

Dose. The first dose is 500 or 1000 millions (according to which of the two Typhoid-Paratyphoid vaccines is used), followed in ten days by the second dose, of 1000 or 2000 millions, and after another ten days by the third dose, of 1000 or 2000 millions, thus completing the treatment for immunization.

The contraindications would be the presence of fever, or any departure from the normal health of the patient, and in women the presence or near approach of the menses.

Typhoid-Paratyphoid Vaccine is supplied in four packages — containing respectively three bulbs, thirty bulbs, one syringe, and three syringes. In the three-bulb and three-syringe packages one of the bulbs or syringes contains an initial dose, and the other two the second and third doses; in the 30-bulb or "hospital" package, ten of the bulbs contain initial doses, and twenty the successive doses; while the single syringe package contains 2½ Cc., each cubic centimeter representing 1000 or 2000 millions, as the case may be. The bulbs are all rubber-stoppered and the syringes graduated—so the vaccine can be administered fractionally to children from either bulbs or syringes, or in successive doses to adults from the 2½-Cc. syringe.

URETHRITIS VACCINE COMBINED

(URETHRITIS BACTERIN COMBINED).

Each cubic centimeter contains killed cultures of Staphylococcus pyogenes albus, 150 millions; Micrococcus gonorrheæ, Micrococcus catarrhalis, Bacillus coli communis, Bacterium pseudo-diphtheriæ, Streptococcus pyogenes, Staphylococcus pyogenes aureus, and Staphylococcus pyogenes citreus, of each 50 millions—total, 500 millions. Each of these eight organisms is represented by several separate strains.

Therapeutics. It is now an established fact that in chronic cases of gonorrhea one or more of the organisms contained in this vaccine are found associated with the gonococcus in continuing the inflammation and discharge. The vaccine is intended to be used in cases of subacute and chronic gonorrhea in which secondary infection is present.

Dose. A safe initial dose is 250 millions, to be gradually increased to 500 millions as the tolerance of the patient will allow. The clinical conditions will be found a safe guide to both the size of the dose and its repetition. From three to five days is usually a suitable interval between doses.

Urethritis Vaccine Combined is supplied in rubber-stoppered bulbs and graduated syringes, the bulbs in packages of four and the

syringes in packages of one and four; also in bulk packages of 5 Cc. and 20 Cc.

METHODS OF ADMINISTRATION OF VACCINES.

The hypodermatic injection is the most usual method, and the only one regarded as of established value. By this method absorption is rapid and the dose is accurately regulated, owing to the fact that the whole amount injected is absorbed.

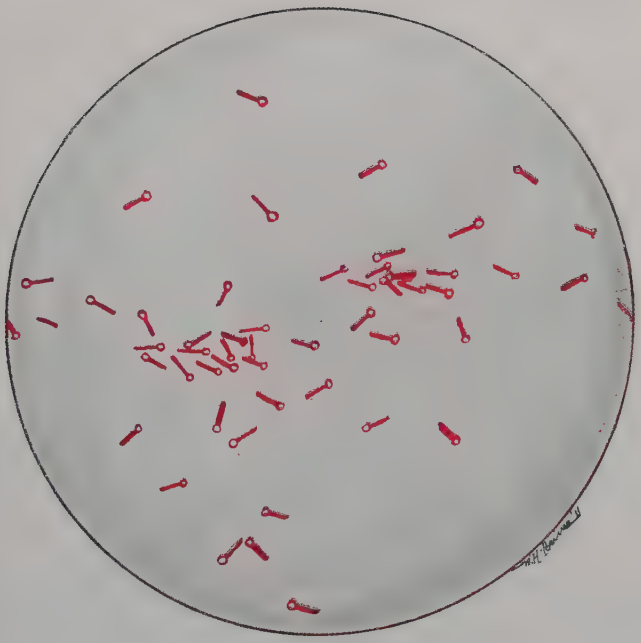
The injection may be made in the flank, the scapular or deltoid region, or the forearm, and it should be made under the strictest aseptic precautions.

Rectal injections have been recommended but are of doubtful value. Larger doses would be necessary, owing to the fact that not only is absorption slow, but a variable amount only is absorbed.

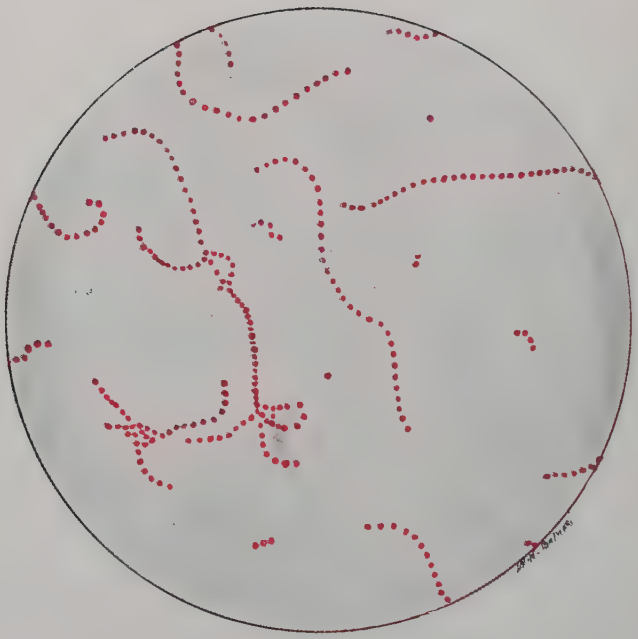
Oral administration has been practiced to some extent and successfully, and in such cases a combination of normal horse serum with the vaccine is advised, thereby securing more favorable results. The dose should be given when the stomach is empty and should be larger than that given hypodermatically.

VACCINE VIRUS (SMALLPOX).

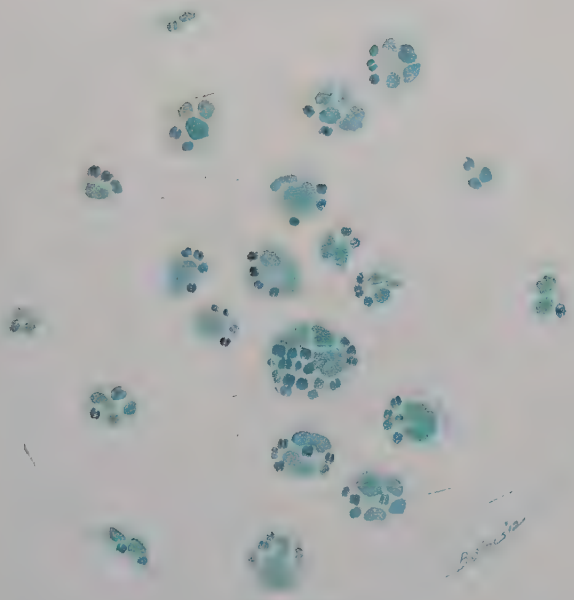
The term "vaccine" applies, primarily, to the refined virus from bovines, employed in vaccination against smallpox, in which by



Bacillus tetani with spores. x 1000.
Drawing from cover-slip preparation.



Streptococcus pyogenes—plate culture. x 1000.
From drawing.



Meningococcus in pus. x 1000
Gram's method. Hasten decoloration of tissue cells in which the cocci may be imbedded by adding 3 per cent nitric acid to the alcohol and then wash in pure alcohol. All the tissue cells are decolorized and the bacteria are stained a deep-blue. This method is of diagnostic value.

Bacillus Bulgaricus x 1000

inoculating the body with modified cowpox virus the vaccinated subject is immunized against smallpox.

In former years vaccine was made in stables, and no special care was taken to free the virus from pathogenic bacterial contamination.

To-day, Parke, Davis & Co. prepare glycerinated vaccine from the vesicles that form on healthy young heifers previously inoculated with the virus of cow-pox. Each animal passes a rigid veterinary inspection. In due time the vesicles are removed in the operating room under conditions of absolute cleanliness and asepsis, the work being done by experts and everything involved in the technique being sterile. OUR VACCINE VACCINATES; it yields, in other words, the maximum percentage of *takes*. The references to it by a host of practitioners are of the most complimentary nature.

To a certain extent the propagators of vaccine virus are at the mercy of transportation companies and druggists, since no matter how carefully this material is prepared for the market it is subject to injury by excessive heat. We take all practicable precautions to safeguard our vaccine in shipment and storage, but, after all, a good deal depends, in hot weather especially, upon conditions beyond our control. The physician need not, of

course, be urged to keep his vaccine stock in a cool place.

Our Vaccine Virus is supplied in two forms: in hermetically sealed capillary glass tubes and in large glass tubes fitted with two compartments, one containing an ivory point and the other a liberal supply of vaccine. The capillary tubes are packed in cases containing five, together with a rubber bulb for expelling the lymph and a needle for scarifying. The points are packed in boxes of five, each in a glass tube by itself, as previously described.

Section 5.

DIAGNOSIS.

THE DIAGNOSIS OF TYPHOID FEVER.

THE WIDAL TEST.

The Widal test depends upon the fact that if a small amount of blood, or blood-serum, or a very small portion of the breast milk, or even tears, from a patient having or recently having had typhoid fever, be brought in proper dilution in contact with living typhoid bacilli, these organisms soon lose their motility and gradually agglutinate. The agglutinizing property is transmitted from mother to child by means of the milk, and the typhoid bacillus when present in the fetus produces agglutinins in its blood.

The typhoid bacilli used in the test are those grown on artificial media, not such as have been recently isolated from a case of typhoid fever. Freshly isolated cultures may not agglutinate as readily as an old stock laboratory culture.

When the test is to be used, a culture inoculation is made in broth-bouillon and incubated for twenty-four hours at a temperature of 37° C. From this test culture a proper dilution is made by adding the bacilli to blood serum

diluted with normal salt solution after the following method: The finger tip or lobe of the ear is pricked, the blood drawn and centrifugated, and with a pipette of a red blood-cell counting apparatus the serum is drawn up to the mark 1.0. Then the pipette is dipped in physiologic salt solution, and the liquid drawn up till the figure 21 is reached. This gives a dilution of 1:20. One drop of the bouillon culture and one drop of the diluted blood serum are then placed on a cover-glass, which is inverted over a hollow slide and the drop examined.

This makes a serum dilution of 1:40. The time for complete reaction to take place is about 20 minutes. A positive reaction means absolute immobilization of all the bacilli, and the clumping of most of them.

This is an exceedingly accurate test when properly employed, but has one disadvantage in that it does not show the reaction until about the seventh day of the disease, or in some cases not until the twelfth day.

THE AGGLUTINATION TEST WITHOUT A MICROSCOPE.

Not long after Widal's discovery Bordet found that typhoid bacilli continued to be susceptible to clumping or agglutination after having been killed by means of some antiseptic. One important aspect of this discovery

lay in the fact that, while live cultures must be of a certain age (12 to 24 hours) to agglutinate satisfactorily, the killed cultures preserve their susceptibility to agglutination indefinitely. Other points in favor of killed cultures are: The absence of all danger of infection, the greater uniformity in the reaction, and the impossibility of bacterial growth occurring while the test is in progress—such growth in live cultures very often obscuring the reaction.

Widal and Gruber observed that the clumping effect of typhoid blood-serum on typhoid bacilli could be seen in a fluid culture in a test tube. When typhoid serum is added to a tube containing a suspension of typhoid bacilli the same phenomenon occurs as the one we see under the microscope. Several bacilli begin to adhere to each other, these aggregations becoming larger and larger until they become visible to the naked eye. If the reaction be closely observed in its successive stages, it will be noted that the fluid in the tube, which before the addition of the serum presented a homogeneous slightly cloudy appearance, takes on a granular aspect, and that the granules increase in size or coalesce to form small floccules, growing to good-sized flakes, which, after some time, settle down to the bottom of the tube as a white precipitate, leaving the supernatant fluid perfectly clear.

THE NEW METHOD.

This new method of making the agglutination test, by means of killed cultures in narrow test tubes, called the *macroscopic* in contradistinction to the old or microscopic method, has gradually grown in favor, and is now made use of in preference to the older method in nearly all laboratories where considerable work on agglutination is carried on.

The principles involved in these later discoveries have been embodied in our TYPHOID AGGLUTOMETER, an apparatus with which an accurate diagnosis of typhoid fever can be made without the use of either a live culture or a microscope.

We are marketing two styles of Agglutometer, which we have designated No. 1 and No. 2.

AGGLUTOMETER NO. 1.

This outfit consists of:

(a) Four tubes containing a sterile permanent suspension of typhoid bacilli; three to be used in making the test, the fourth, to which no serum is added, serving as a control for comparison of reactions.

(b) Blood-collecting apparatus (blood-tube and lancet).

(c) Tube in which the serum is to be diluted before adding it to the suspension.

(d) Pipette for distributing the serum.

In performing the test the serum dilution is

distributed in graded quantities to three tubes of suspension. The rapidity of the reaction depends upon both the agglutinating power of the blood-serum and the temperature at which the tubes are kept. The tubes should be examined at the end of the first hour, then three hours later, and again if necessary on the following day. When the reaction is positive, floccules appear in one or more of the tubes. These floccules are small at first and disseminated through the fluid; they gradually increase in size, and in some cases settle to the bottom of the tube.

In a *complete* reaction the supernatant fluid has cleared.

In a *positive but incomplete* reaction, floccules are seen in the still cloudy fluid.

In a *negative* reaction, the fluid in the tubes remains uniformly clouded as in the control.

Typhoid Agglutometer No. 1 contains sufficient material for one three-tube test only. Although a satistactory diagnosis can often be made by using only one tube, employing a serum dilution of 1:50, a three-tube test showing the effect of the serum in low, medium and high dilutions (1:50, 1:100 and 1:200) is more convincing, exhibiting, as it does, not only the fact of typhoid infection, but the degree of the development of "agglutinin" in the patient's blood. A high dilution alone, if it exhibited any reaction, would afford positive proof of

the typhoid character of the serum; but it might possibly fail to show a reaction when a lower dilution would have done so.

AGGLUTOMETER NO. 2.

This outfit differs from Agglutometer No. 1 in the fact that a larger amount of suspension (a one-ounce bottle, sufficient for making from ten to thirty tests, depending upon the number of tubes used for each test) is supplied. It also contains a graduated pipette for distributing the suspension, and is marketed in a neat and durable box.

Although this form of apparatus necessitates a slightly increased initial outlay, the number of tests which it is possible to make with it reduces the expense of individual diagnoses to about one-fourth of what it is when outfit No. 1 is used. The quantity of suspension which we recommend filling into each tube for the test is 20 drops, or .75 Cc. The bottle contains one ounce, or approximately 30 Cc., of suspension. The control tube, filled once, will serve for comparison in all the tests; no serum is added to the suspension placed in this tube, hence no change occurs in its appearance.

Although a three-tube test, employing different dilutions in each tube, is advisable, as explained under a previous heading, a fairly satisfactory diagnosis can be made by the use

of but two serum dilutions, or even a single dilution.

If three tubes are used the material will be found amply sufficient for making ten tests; if two tubes are used, twenty tests can be made; and if one tube only, thirty tests.

Complete directions for using the Typhoid Agglutometers accompany each outfit.

THE VALUE OF THE TEST.

An agglutination is obtained by the macroscopical method (that is, the method followed when the Agglutometer is used) in all cases where the old microscopic method will give a positive result.

In general it may be said that whenever a positive reaction occurs in a dilution of 1-100 it implies the existence of typhoid fever. Abbott (*Philadelphia Medical Journal*, Feb. 25, 1899) studied 4154 cases and found the percentage of error only 2.8 per cent. The test is said to be of special value in the case of children. Gershel (*Medical Record*, Nov. 26, 1901), among 84 cases of typhoid fever in infants, found the reaction positive in 81, while it was negative in 115 patients who were suffering from other diseases. One precaution is necessary in drawing diagnostic conclusions from a Widal test. If you obtain a negative reaction, do not conclude that typhoid fever is absent, but make a second or even a third test at intervals

of one or two days. In some cases the principle in the blood which causes clumping of the bacilli, called agglutinin, is not present in sufficient amount to produce agglutination until some days after the commencement of the disease. From the mass of evidence which has been presented it is difficult to draw any definite conclusion as to the exact day of the disease at which the agglutination reaction can first be expected. Statistics show that in over 93 per cent. of cases the reaction may be expected to appear before the end of the first week in bed. Many cases will react positively during the period of malaise, before the patient has as yet taken to bed.

A USEFUL INSTRUMENT.

The Typhoid Agglutometer will undoubtedly popularize the Widal test and extend the usefulness of this valuable diagnostic aid. It is already the subject of much favorable comment. Joseph McFarland, M.D., Professor of Pathology and Bacteriology, Medico-Chirurgical College, Philadelphia, writes as follows:

I wish to express approbation of your new device known as the Typhoid Agglutometer. It seems to me that the profession can scarcely sufficiently appreciate this means of making an accurate diagnosis of typhoid fever at the bedside. Heretofore the application of the Widal method has required a considerable knowledge of laboratory technic, proprietorship of apparatus, manufacture of media, and time-consuming manipulations, or has required that the blood of the patient be sent to some distant point from which a delayed

report has often been anxiously awaited. We now find that for a very moderate expenditure of money and patience, an accurate diagnosis can be made in a few hours at the bedside with materials readily prepared, unlikely to deteriorate, innoxious to handle, and simple to manipulate. There is now no reason why a practitioner of medicine in the most remote corner of the country shall not conduct as scientific an observation and make as accurate a diagnosis of typhoid fever as one in the heart of a great city surrounded by laboratories and other facilities.

EHRLICH'S DIAZO-REACTION IN TYPHOID FEVER.

This test depends upon the fact that in typhoid fever the patient's urine contains a chromogen which, when treated with diazobenzene sulphonic acid and ammonia, produces a distinct red hue in the urine. It is present usually as early as the sixth day, and lasts until about the eighteenth day. The test consists in using two solutions—one a 5-per-cent. solution of hydrochloric acid to which is added sulphanilic acid in the proportion of 1 gramme for each 100 Cc.; the other a 0.5-per-cent. solution of sodium nitrate. When the test is made the two solutions are mixed in the proportion of 40 to 1. Equal portions of this mixture and urine are then shaken together and rendered alkaline by the addition of ammonium hydrate, which is allowed to flow down the side of the tube, forming a layer above the contained mixture. If typhoid fever is present a garnet-red hue develops. After standing for some time a green sediment forms which Ehrlich considers characteristic of a true reaction.

Ehrlich's diazo-reaction can always be obtained at the height of an attack of typhoid fever; it is permanently absent only in the milder cases. In severe cases, when improvement begins to take place, the reaction not rarely disappears, so that from this sign favorable conclusions may be drawn at a time when other symptoms are not indicative of improvement. In relapses from typhoid fever the diazo-reaction, if it has already disappeared, generally returns, while it does not reappear when fever occurs during convalescence from typhoid fever as the result of organic disturbances due to other causes.

THE BORDET-GENGOU REACTION.

This is a biochemical reaction which turns to clinical account the diagnosis of certain bacterial infections by the cytolytic phenomena. In utilizing this reaction in the diagnosis of typhoid fever, the mode of procedure is as follows:

Five substances are required to perform the test: (*a*) Typhoid antigen. This is an emulsion of killed typhoid organisms. (*b*) The serum from a typhoid fever patient, which is heated to a temperature of 55°-60° C. for half an hour. This contains the typhoid amboceptor. (*c*) The blood serum from a guinea-pig. This provision is known as the complement. (*d*) The hemolytic serum, which

is obtained by immunizing a rabbit with the red corpuscles of another animal, *e.g.*, the sheep. This rabbit's serum will then cause hemolysis of sheep's corpuscles *in vitro*. The serum is heated to destroy the complement. (*e*) The suspension of sheep's corpuscles in normal saline.

The first three substances are placed in a sterile test tube, which is well shaken and then placed in an incubator at 57° C. for one hour. The complement will be found to have united firmly to the typhoid amboceptor and typhoid antigen, which are now represented as the emulsion of typhoid organisms.

The hemolytic serum, suitably diluted, and the sheep's corpuscles are then added, and the whole thoroughly shaken. An opaque red fluid results. The tube is then placed for about two hours in an incubator at a temperature of 57° C., with the result that the red corpuscles will have sunk to the bottom of the tube, having undergone no hemolysis, and the fluid in the tube remains colorless.

A control is made by preparing another tube, in which the serum of the typhoid patient is replaced by that of a normal individual. The same incubation is carried out, but with different results. The fluid has become completely laked and the red blood-corpuscles seem to be destroyed, the solution in the tube being of a transparent red color.

The hemolysis here has been complete because the complement, not being anchored to the typhoid amboceptor and typhoid antigen, is free to fix itself to the hemolytic amboceptor and red corpuscles, thus constituting a hemolytic system.

GONOCOCCUS ANTIGEN

For the Complement Fixation Test in the Diagnosis of Gonorrhea.

This antigen is a neutral extract of pure cultures of gonococci, prepared from multiple strains of the organism. These strains represent several groups of gonococci according to the classification of Dr. John C. Torrey, of the Loomis Laboratory, New York City. The test offers the greatest possibilities and has the greatest value in those cases in which the diagnosis is uncertain or obscure, and in the subacute stage when it is impossible to demonstrate the Micrococcus gonorrhœæ in smears from the discharge. A positive reaction is to be expected in chronic stages with sequelæ when products of the gonococcus are still present, either alone or associated with a secondary infection.

The paraphernalia of the actual test comprises six tubes, the first containing the patient's serum, together with antigen, complement, corpuscles and amboceptor; the second con-

taining normal serum, antigen, complement, corpuscles and amboceptor; a third containing positive serum from a case of gonorrhea, antigen, complement, corpuscles and amboceptor; and a fourth, fifth and sixth tube containing patient's serum, normal serum, and positive serum respectively, together with all the other ingredients except the antigen.

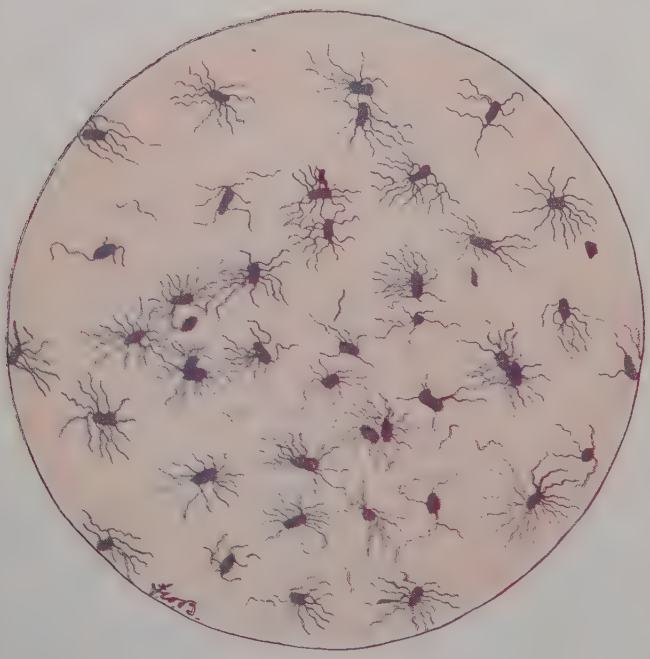
COLLECTING THE REAGENTS FOR THE TEST.

The diagnostician must have: (*a*) About 1 Cc. of blood from a patient presenting a case of positive gonorrhea, and the same amount from a known normal individual to be used as a control. The serum is separated from the clot by means of a centrifuge, or by natural contraction of the clot in a cool room, and is then pipetted to small tubes and heated in a water bath at 56° C. for one-half hour. (*b*) The gonococcus antigen is supplied ready for immediate use. (*c*) Just prior to making the test, bleed a medium-sized normal guinea-pig and separate the serum from the corpuscles (this serum represents the complement). (*d*) The blood of a normal sheep is collected in normal salt solution containing 1 per cent. of sodium citrate, which is centrifugalized, the supernatant solution drawn off with a pipette and the corpuscles twice washed with physiologic salt solution, being centrifugalized after each washing. The supernatant liquid having

been removed, 1 Cc. of the centrifugalized corpuscles is added to 99 Cc. of sterile physiologic salt solution; this suspension, if kept in a refrigerator, may be used until it shows evidence of hemolysis. (*e*) Antisheep hemolytic amboceptor, furnished ready for use, must be used according to its labeled strength, which indicates the amount to be employed as one unit.

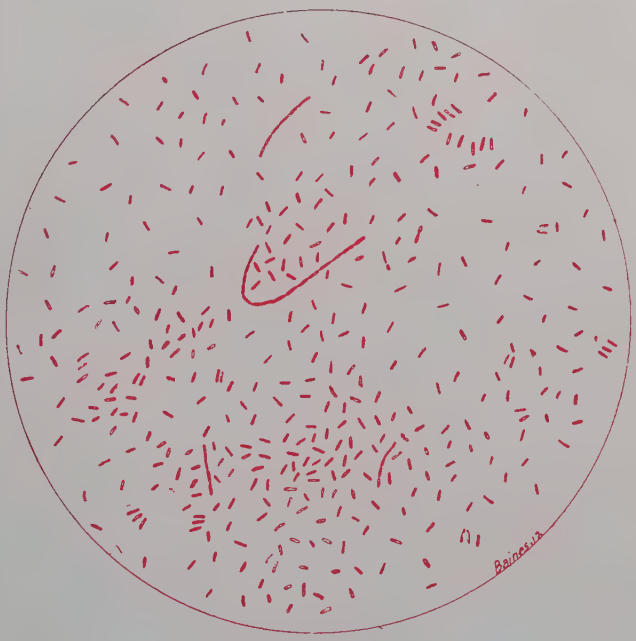
MAKING THE TEST.

The reagents are to be mixed in glass tubes of a capacity of about 2 Cc. (9 mm. in diameter) in the following order, the amounts in each tube being measured accurately: (*a*) One drop (from a 1½ mm. pipette) of the patient's serum prepared as above described; (*b*) one drop (from a 1 mm. pipette) of gonococcus antigen; (*c*) one drop (from a 2½ or 3 mm. pipette) of fresh normal guinea-pig serum; incubate twenty minutes at 37° C. in incubator or water bath; then add (*d*) 1 Cc. of a 1-per-cent. saline suspension of washed red blood-corpuscles of sheep, prepared as above described, and (*e*) one unit of antisheep hemolytic amboceptor. Let stand for fifteen minutes at room temperature and record results. In like manner are prepared the tubes containing the serum of the normal control and of the positive gonorrhea case. The repetition is made by preparing three other tubes



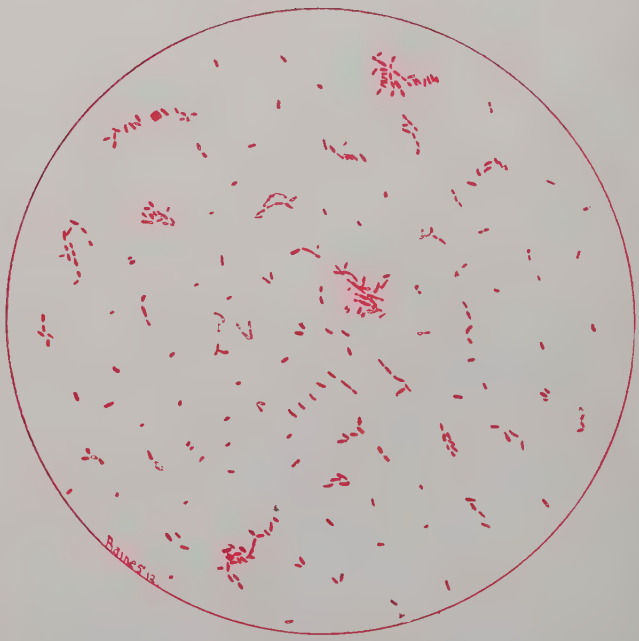
Bacillus typhosus showing flagella. x 1000.

Bacterium tuberculosis from sputum. x 1200.
Drawing from cover-slip preparation.



Bacillus typhosus x 1000

Bacillus typhosus stains easily with anilin dyes, but readily decolorizes. Cover-glass preparations stain well with aqueous solution of fuchsin. Wash in water, not in alcohol.



Bacillus acne, x 1000

in like manner, except that the gonococcus antigen is omitted.

RECORDING THE REACTION.

In recording the reaction, the contents of the tube containing the known positive serum will remain unchanged; the corpuscles in the tube containing the negative control serum will undergo dissolution (hemolysis); and if the contents of the tube containing the patient's serum remain unchanged a positive reaction is indicated, while if hemolysis occurs a negative reaction is recorded. The three tubes which do not contain gonococcus antigen should hemolyze before or about the time the corpuscles in the normal control tube undergo hemolysis.

EXPLANATION OF THE REACTIONS.

The above reactions are explained by the theory that the serum from a positive gonorrheal case contains antibodies which combine with the antigen by the aid of the complement, which is fixed in this reaction. In the serum from the normal control, which contains no antibody, the complement remains unchanged during the incubation and possesses the power to combine with the sheep corpuscles and antisheep amboceptor, thus causing dissolution or hemolysis of these corpuscles. In the three tubes containing no gonococcus antigen,

the first combination is impossible, consequently hemolysis always occurs.

Parke, Davis & Co. are prepared to furnish the Gonococcus Antigen and the Antisheep Amboceptor, accurately standardized, in 1-Cc. glass bulbs, the Antigen in packages of six bulbs, the Amboceptor in single bulbs. Each bulb contains sufficient material for making fifteen or sixteen tests, the Amboceptor bulbs fifteen to twenty times this number if the cases can be grouped so that none of the material need be thrown away.

THE WASSERMANN REACTION.

The Wassermann reaction is one that can only be elicited with assurance of accuracy by a skilled laboratory worker; nevertheless every physician should know its significance and the general facts concerning it.

A positive reaction may occur in cases of recent malaria, yaws or leprosy. That alcohol in considerable quantities may mask an otherwise positive reaction, and that the administration of antisyphilitic drugs should be suspended for three to six weeks before giving the test, are the conclusions of competent observers.

The reaction is obtained as follows: Select a prominent superficial vein, preferably at the bend of the elbow. Cleanse the skin and let

it dry. Puncture the vein through the skin with a *dry*, sterile needle. Discard the first few drops and half fill a *dry*, sterile test tube of medium size. Allow no water to enter the tube, as it may interfere with the reaction. Keep in a cool place.

To draw the cerebrospinal fluid, tap the subarachnoid space in the interval between the fourth and fifth lumbar vertebræ. Let the patient lean well forward to widen the interval, introduce the needle one-half inch below and to the outer side of this spinous process, and pass it forward and inward for a depth of about three and a half inches. Sudden cessation of tissue resistance indicates the entrance of the needle point into the subarachnoid space. Draw a few cubic centimeters of the fluid, and handle with the same precautions as in the case of the blood.

The reaction as performed in the Wassermann laboratory to-day requires five reagents:

1. Serum of patient heated at 56° C. for one-half hour.

2. Antigen—extract of luetic liver or beef heart.

3. Amboceptor—serum of rabbit which has been immunized against sheep corpuscles.

4. Complement—fresh serum of guinea-pig, diluted one to ten in salt solution.

5. Washed blood cells of sheep—solution of one to twenty in salt solution.

If sheep's blood-corpuscles, amboceptor and complement are placed in a test tube, after a short time the corpuscles are destroyed and the fluid becomes perfectly clear. This is known as hemolysis.

Syphilitic serum contains the antibodies of syphilis. Normal serum does not. *A definite quantity* of serum, antigen and complement is placed in the water bath for one-half hour at 37° C. If the serum contains the antibodies of syphilis the complement soon becomes used up or fixed so that it no longer remains free. With a negative serum (no antibodies) the complement remains free. This is the first step of the Wassermann reaction.

The tubes are then removed from the water bath, *definite quantities* of amboceptor and sheep's blood are added, and the tubes are again placed in the bath. After a short time, if the complement has remained free, it acts with the amboceptor and destroys the blood-corpuscles, the liquid clears, and hemolysis is said to have taken place—a negative reaction. If the complement has not remained free, hemolysis does not occur; the liquid remains cloudy —a positive reaction. Degrees of cloudiness are designated as weakly or strongly positive. If the liquid does not quite completely clear, the reaction is described as doubtful.

TOXINS, CULTURE PRODUCTS, ETC.

COLEY'S MIXTURE

(Erysipelas and Prodigiosus Toxins).

Dr. Wm. B. Coley, of the New York Cancer Hospital, having observed that sufferers from malignant growths were apparently cured by an attack of erysipelas, adopted the practice, in inoperable cases of malignant neoplasms, of injecting a mixture of the toxins of Streptococcus erysipelatis with those of the Bacillus prodigiosus.

The Streptococcus erysipelatis, after a three-weeks growth, is inoculated with the Bacillus prodigiosus, and the mixed culture is allowed to incubate ten days longer; it is then bottled and sterilized by heating for one hour at 60° C. The preparation, being unfiltered, is turbid in appearance.

Therapeutics. Dr. Coley advocates the use of these toxins in all cases of inoperable sarcoma (except the melanotic), also as a prophylactic against recurrence after operations for primary sarcoma (after the healing of the wound).

Dose. In the commencement of treatment a daily dose is injected into the buttocks or pectoral region, of ¼ minim of the fluid

diluted with sufficient boiled water to make apportionment of the quantity. After the individual susceptibility has been ascertained, each subsequent dose is increased by ¼ minim until the required reaction is secured—*i.e.*, a chill followed by a temperature of 102° to 104° F. When this stage is reached no further increase in the dose is made until it fails to give the required reaction, at which time the dose is again increased as before. If the tumor is in an accessible region it is a good plan to give alternate injections into the buttocks and into the tumor itself.

Erysipelas and Prodigiosus Toxins are supplied in packages containing five 1-Cc. bulbs, rubber-stoppered; also in 15-Cc. bottles.

BACILLUS LACTIS BULGARICUS (Tablets).

The unusual longevity of the peasants of Bulgaria is quite generally known and is attributed largely to the fact that these people depend upon sour curdled milk as a major part of their diet. This sour milk so generally consumed by them goes by the name of Kisselo-mleko and is made from day to day by using a starter which they call Podkvassa.

Investigations into the nature of Kisselo-mleko and the reason for its purported effect on the length of human life have revealed the presence of three predominating kinds of

Drive at Rhodale Farm

Wooded Section at Rhodale Farm

micro-organisms which give the beverage its distinctive flavor and consistency. Cows' milk treated with these three types of bacteria, both synthetically and collectively, duplicates Kisselo-mleko.

Of the three organisms isolated, one, considered of greatest value in correcting intestinal disorders, produces a curdled milk similar to Kisselo-mleko, but with a somewhat stronger acid taste. To this organism, named Bacillus Bulgaricus, is attributed the power of displacing the objectionable putrefactive organisms in the lower intestine. By exact determination of the nature of the bacterial content of fecal matter before and after taking Bacillus Bulgaricus it has been demonstrated in a number of cases that the change from the putrefactive forms to the beneficial lactic acid bacilli is almost complete within three to four days after the bacilli are ingested. Experiments seem to show that several of the weaker types of lactic acid bacteria are destroyed when taken into the stomach and never reach the lower intestine, where the greatest amount of benefit is believed to be derived from the effect of the freshly produced lactic acid.

Therapeutics. These tablets have been found beneficial in diseases due to intestinal autointoxication. Recently Dr. Ralph O. Clock, of New York, reported the successful

treatment of 116 cases of infantile diarrhea out of a total of 117, by the administration of tablets composed of a culture of the Bacillus lactis bulgaricus, at the Babies' Hospital, New York City. In severe cases as many as forty-two tablets were given in twenty-four hours, and to very young babies.

An average dose is one or two tablets every two to three hours, to be continued for three or four days. The treatment is to be repeated as clinical indications seem to warrant.

Bacillus Bulgaricus tablets are supplied in vials of 25 and bottles of 100.

LACTONE.

Lactone is a viable culture, in tablet form, of the Milchsauerbacillus of Hueppe, the organism concerned in the natural souring of milk. It is designed for the production of a superior quality of buttermilk, for the benefit especially of infants who cannot take other foods and whose mothers cannot nurse them, and for the dietetic treatment of intestinal disturbances of various kinds. Lactone Buttermilk is, as well, a delicious beverage for people in perfect health. When the tablets, crushed, are added to whole sweet milk diluted with water and warmed to a temperature of about 80 degrees, the organisms grow rapidly, developing lactic acid as they grow; but instead of this development giving the milk the quality

of ordinary sour milk, it imparts the peculiar flavor of freshly churned buttermilk. Directions for use are, of course, supplied with each package marketed. The tablets are put up in bottles of 10, 25 and 100.

SUPPOSITORIES OF LACTIC ACID BACTERIA.

For the treatment of non-specific vaginitis, cervical erosion, leucorrhea, or any non-specific catarrhal or inflammatory condition of the vaginal tract, we supply an olive-shaped suppository containing a pure culture of lactic acid bacteria. One suppository is to be inserted in the vagina at night, upon retiring. Either the bacteria themselves or the nascent acids formed by them as they grow have the effect of toning up the mucous membrane by antagonizing the pathogenic bacteria present—though in specific infections, as by the gonococcus, other treatment will be required. The suppositories are marketed in boxes of 12, twelve boxes in a package.

COAGULOSE, P. D. & CO.

(Hemostatic Ferment).

It has long been recognized that persistent hemorrhage may be due to a variety of causes, one of which is diminished or retarded blood coagulation. This is believed to be due, in the majority of cases, to the insufficient pro-

duction of a specific substance known as "thrombin" (fibrin ferment), which, acting on the fibrinogen, forms fibrin, the essential element in blood coagulation. Many cases of hemorrhage have been successfully controlled by the local application or the hypodermatic injection of fresh normal blood or blood serum. The use of serum for this purpose has not, however, found as wide an application as the results reported warrant, owing to the difficulty of procuring fresh and reliable serum on short notice. Fluid blood serum cannot be preserved for any great length of time for this purpose, since it rapidly loses its efficacy as a hemostatic.

Coagulose is obtained by precipitating normal blood serum. It is a sterile, soluble, anhydrous powder, containing the fibrin ferment necessary for clotting the blood. It is readily soluble in cold water at concentrations two or three times that of the original serum; and it possesses over fluid blood serum the great advantage of retaining its activity unimpaired for long periods of time.

Coagulose, being permanent, readily available and easily applied, eliminates the delay associated with the preparation of fresh fluid serum, a delay which may prove fatal.

Therapeutics. Used in the treatment of hemorrhage due to defective clotting of the blood, as seen in hemophilia, hemorrhage of

the new-born, also nasal hemorrhage, hemorrhage of gastric and duodenal ulcer, hemorrhage from the kidney, the bladder and the uterus, pulmonary and puerperal hemorrhage, and after turbinectomies and tonsillectomies; also as a styptic to bleeding surfaces, oozing after nasal operations, and as a prophylactic before operations upon the nose and throat.

Administration and Dosage. Coagulose is injected subcutaneously; in general the dose consists of the contents of one bulb, but the amount may be increased or diminished as indicated. If bleeding is not controlled within half an hour, a second dose should be given. In serious cases a second dose should be injected regardless of the results of the first dose; in persistent hemorrhage three or four doses should be injected daily for several days, and injections should be continued for a short period after the hemorrhage ceases. As the substance is non-toxic the dose is the same for infants as for adults.

DIRECTIONS FOR PREPARING COAGULOSE FOR USE

Add to the powder in the bulb 6 to 8 Cc. of sterile water, the temperature of which should not be above 98° F. Introduce the water into the bulb through the needle of a hypodermatic syringe. The rubber stopper should then by replaced and the bulb immediately shaken, continuing the agitation three or four

minutes or until the powder is completely dissolved.

To fill the syringe, *invert the bulb* and remove the rubber stopper from its mouth. Insert the needle of the syringe into the solution in the inverted bulb and draw the fluid into the syringe.

By inverting the bulb before inserting the needle, one avoids the likelihood of drawing the foam or bubbles (caused by agitating the liquid in the bulb) into the syringe, as the foam will rise to the top of the solution, leaving the field for the insertion of the needle perfectly clear.

Coagulose is supplied in 15-Cc. glass bottles which contain 0.65 gramme of the desiccated powder.

PHYLACOGENS.*

GENERAL DESCRIPTION.

Since 1910 much interest has been excited in medical circles by the reports of the extraordinary results following the use of a new form of bacterial derivative in the treatment of acute and chronic infections. This derivative was originated by Dr. A. F. Schafer, of Bakersfield, California, who first presented his discovery to the profession through the San Joaquin Medical Society, at Fresno, California, in October, 1910, and later through the San Francisco Medical Society on January 14, 1911. Dr. Schafer's preliminary paper was published in the *Therapeutic Gazette* for April, 1911.

Parke, Davis & Company, before undertaking the manufacture of Phylacogens, first made a searching and critical investigation of all the circumstances surrounding the work in California. Several competent attachés of our scientific departments personally called on physicians and visited the hospitals in which the cases were treated, and witnessed the unique results obtained in a large number

*The word "Phylacogen" distinguishes the modified bacterial derivatives prepared by Parke, Davis & Co. according to the method of Dr. A. F. Schafer.

of them. The preparation of the Phylacogens was then begun (1911) in the Parke, Davis & Company Biological Laboratories in Detroit. At first this work was done under the personal supervision of Dr. Schafer, and later in accordance with his written instructions.

THEORY: THE VIEWS OF DR. SCHAFER.

The principle upon which the use of these Phylacogens is founded is, briefly, the theory of multiple infections. The principle is supported by an extraordinary practical experience, supplemented by exhaustive and long-continued clinical experimental work by Dr. Schafer.

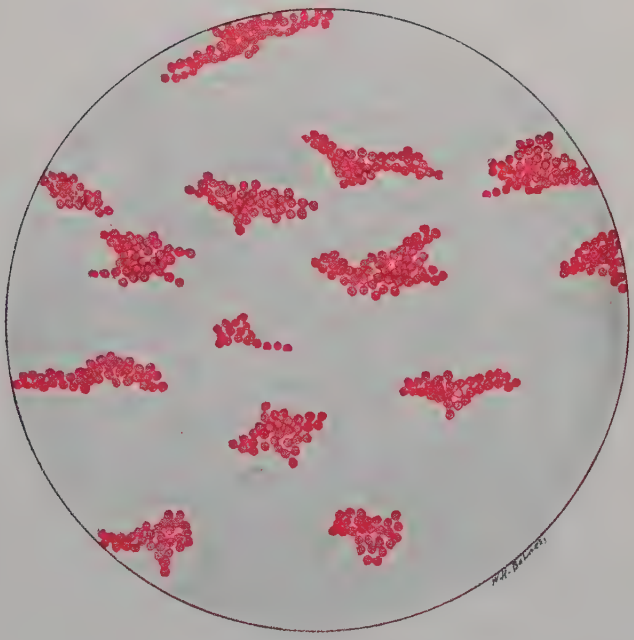
Three facts are set forth by Dr. Schafer as the basis of this new therapy:

First: Practically all acute and many of the chronic diseases are caused by the metabolic products of pathogenic bacteria.

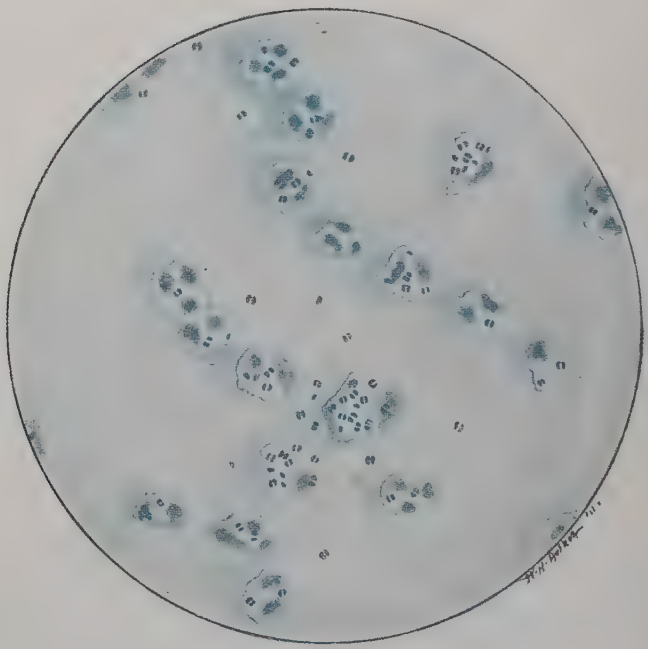
Second: The human subject is the host of micro-organisms that are pathologically latent, but capable of setting up a disease process under certain conditions.

Third: The growth of infecting micro-organisms can be arrested and their effects neutralized by products derived from their development in artificial culture media.

Dr. Schafer is of the belief that all infections are "mixed infections;" that, except in rare instances, there is no such thing as an



Staphylococcus pyogenes aureus. x 1000.
Drawing from cover-slip preparation.



Micrococcus gonorrheæ from pus. x 700.
Drawing from cover-slip preparation.

Acne vulgaris – pustules. 9

A Comparison of Degrees of the Cutaneous Reaction
(von Pirquet's method)

1. Inoculation with Undiluted Tuberculin Old.
2. Dilution of Old Tuberculin 1:4.
3. Dilution of Old Tuberculin 1:16.
4. Dilution of Old Tuberculin 1:64.
5. Control.

infection by a single species of micro-organism; that while one species may predominate, the pathogenic process engendered by it is accelerated and intensified by the presence of organisms of other species; in other words, that in the course of an infectious disease the symptoms are due not only to the effects of a single species of organism (the specific infection), but to the influence of other organisms whose pathologic rôle is not insignificant, but must be reckoned with in any successful scheme of therapeutics.

It is Dr. Schafer's opinion that the great variety of micro-organisms harbored by the human organism without harm to itself during periods of physiological resistance at or above par and in the absence of any solution of tissue continuity, assume pathological significance when the resistance falls below par or when a solution of tissue continuity occurs; furthermore, that certain diseases, as typhoid fever, pneumonia, tuberculosis, erysipelas, rheumatism, and others, while due to the presence of the organisms to which these diseases are usually ascribed, as Bacillus typhosus in typhoid fever, Diplococcus pneumoniæ in pneumonia, Bacterium tuberculosis in tuberculosis, etc., owe a part of their symptoms to the complicating organisms which are always present in great variety and number.

Dr. Schafer points to the fact that bacterial

vaccines not infrequently fail of effect because the truth of the above assumption is not recognized, especially when the treatment consists in the use of a vaccine made from a single species of organism isolated from the patient. Single species vaccines have proved successful in many cases, but the multiplicity of "combined" vaccines now in use points to the conclusion that most patients who require vaccine treatment of any kind require something more than a vaccine made from one organism; and the success attending the use of these vaccines, even when the disease under treatment is apparently due to one species only, lends color to Dr. Schafer's theory.

The term "Phylacogen" has been coined to distinguish the several new bacterial derivatives (devised by Dr. A. F. Schafer and produced by us) from other remedial agents of similar character that may be offered to the medical profession. Each specific Phylacogen is further identified by the prefixion of the name of the pathological condition in which it is indicated—as Gonorrhea Phylacogen, Rheumatism Phylacogen, Pneumonia Phylacogen, etc.

The term "Phylacogen" (derived from two Greek words, *Φύλαξ*, a guard, and *γενναν*, to produce) means "phylaxin producer." Phylaxin is the name applied by Hankin to a defensive proteid found in animals that have

acquired an artificial immunity to a given infectious disease.

PREPARATION OF PHYLACOGENS.

Phylacogens are neither "bacterial vaccines" nor "sera" as ordinarily understood. They are sterile aqueous solutions of metabolic substances or derivatives generated by bacteria grown in artificial media.

The Phylacogens are made from a large number of species of the well-known pathogenic bacteria, such as the several Staphylococci, Streptococcus pyogenes, Bacillus pyocyaneus, Diplococcus pneumoniæ, Bacillus typhosus, Bacillus coli communis, Streptococcus rheumaticus, Streptococcus erysipelatis, etc. The various organisms are present in the material before filtration in approximately equal proportions. The cultures are incubated at 37° C. for seventy-two hours or longer, after which the bacteria are killed and a preservative consisting of 0.5 per cent. of phenol is added to the fluid, which is then filtered through porcelain. The basic Phylacogen, made in this manner, and used in the preparation of the several specific Phylacogens, is named "Mixed Infection Phylacogen." This basic Phylacogen is a "polyvalent" preparation, or Polyphylacogen, for not only is it made from many different species of bacteria, but each type is represented by strains obtained from a variety

of sources, and the cultures are renewed at frequent intervals.

Each specific Phylacogen is prepared by modifying the basic material (Mixed Infection Phylacogen) by the addition of an equal amount of the filtrate obtained by growing and treating the organism considered to be predominant in the pathological condition to be treated; for instance, in the preparation of Rheumatism Phylacogen, the Streptococcus rheumaticus is grown and treated similarly to the several organisms entering into the preparation of the basic Phylacogen. The filtrate obtained from the preparation of the rheumatism organism is added in equal amount to the Mixed Infection Phylacogen, and the resulting product given the specific name, "Rheumatism Phylacogen." A like method is employed in the manufacture of the other specific Phylacogens, such as Pneumonia, Gonorrhea, Erysipelas, etc.

CULTURE AND SAFETY TESTS.

Aerobic and anaerobic tests are made of each lot of Phylacogen prepared, to determine whether the completed product is sterile. Coincidental safety tests of the same preparations are made by injecting relatively large doses subcutaneously into each of a series of animals; if the animals remain healthy the product is passed. A large number of the test

animals are anesthetized, killed, and examined, ten days after injection; in each instance the autopsy discloses nothing more than a faint trace of tissue irritation at the site of injection.

The present use of the Phylacogens, prepared according to the method originated by Dr. A. F. Schafer, may be objected to by some practitioners on the ground of empiricism, and criticized because there is just now no proved scientific explanation of their exact mode of action. We believe the clinical results obtained thus far with the Phylacogens fully justify their use, even in the absence of a plausible theory explaining the method by which the curative action is produced.

Careful investigations have been conducted in our scientific laboratories for the purpose of determining the physiologic effects of the Phylacogens, and to demonstrate their safety when used therapeutically. These researches have been going on without interruption for more than three years, or since the first investigations were begun.

The degree of potency or energy of the Phylacogens has been carefully ascertained by means of experiments on laboratory animals (some eight hundred of which were used in these investigations). The Phylacogens were injected subcutaneously, intravenously, and intramuscularly, and given by mouth. The

results indicate that the average minimum lethal dose (by *intravenous* injection) per kilo of body weight of an animal is 11.9 Cc. By comparison it would therefore appear that the average minimum lethal dose for a man of 150 pounds body weight is about 800 Cc. The suggested *subcutaneous* therapeutic dose is 1 Cc. to 10 Cc. for the average human patient (150 lbs. weight, or 68 kilograms), or 0.015 Cc. to 0.15 Cc. per kilo. The suggested *intravenous* therapeutic dose is ⅛ Cc. to 5 Cc. for the average human subject (see above), or *0.0018* Cc. to *0.073* Cc. per kilo. The comparatively non-toxic action of these Phylacogens, therefore, seems assured.

Extensive studies with laboratory animals were undertaken for the purpose of determining whether anaphylaxis, or dangerous sensitization of animals, could be produced by injecting Phylacogens. No anaphylactic reactions were observed in our experiments.

CLINICAL TESTING.

In order to obtain direct evidence bearing on the practical value of the Phylacogens, a series of searching clinical tests was instituted in March, 1911. Large quantities of the various Phylacogens were submitted to skilled clinicians in different parts of the country, and the investigation thus begun has continued up to the present time.

With an incredulity amounting to suspicion, and with every determination to be no man's dupe, this investigation of Dr. Schafer's claims for his bacterial derivatives (Phylacogens) was begun. A vast mass of work has been done—in the laboratory, on animals, in the hospitals, at the bedside. Literally hundreds of reputable physicians have administered thousands of doses of the Phylacogens for rheumatism, gonorrhea, erysipelas, pneumonia and mixed infections. A cool, critical survey of the clinical results has convinced us that the Phylacogens possess great therapeutic power.

Dose. The initial (the first) dose of any Phylacogen should invariably be given subcutaneously, for the purpose of establishing the tolerance of the individual patient. *Never* give the first dose of Phylacogen in the vein.

Subcutaneous dose. For the average adult, begin with 1 to 2 Cc., repeating the dose daily and increasing each dose by 1 to 2 Cc., according to the physical and nervous condition of the patient, the character of the disease, the extent of involvement, and the promptness with which the patient responds to the treatment. Each patient presents indications of his own, and the dose should be advanced accordingly until the patient is relieved of all symptoms. It is impossible to state the exact number of doses, or the exact quantity in each

dose, required to treat a case to a successful termination; the treatment will vary widely according to the individual. It is seldom necessary to give a patient more than 10 Cc. subcutaneously at a single dose.

Intravenous Dose. The initial intravenous dose, which should always be preceded by one or more doses subcutaneously, should not be more than $\frac{1}{8}$ to $\frac{1}{4}$ Cc., the second dose $\frac{1}{4}$ to $\frac{1}{2}$ Cc., third dose $\frac{1}{2}$ to $\frac{3}{4}$ Cc., and fourth dose 1 Cc.; then increase the dose about 1 Cc. each day, avoiding, if possible, marked constitutional reactions.

If any single dose, either subcutaneous or intravenous, should cause a very marked reaction, it is an indication that the next dose should either *not* be increased or should be slightly reduced, or the interval between doses lengthened by one or two days; then gradually increase the dose at subsequent injections, according to the tolerance of the patient, giving a little less than enough to cause a strong systemic reaction.

Intramuscular Injections. Tests of the efficacy of intramuscular injections have been made, with the result that such injections are not recommended. The great danger of the accidental puncture of a vein has been proved. The rate of speed of the injection for a proper subcutaneous or intramuscular dose is far too rapid for a safe intravenous injection, and in

case a vein were accidentally punctured a severe reaction would undoubtedly occur. Syncope, collapse, and alarming and even dangerous symptoms are very likely to be produced by such methods.

Intracervical Injections. Injections into the muscles of the uterine cervix have been experimentally studied; the results have been similar to those of the usual intravenous injections, and the procedure is not recommended, since intravenous injections are more satisfactorily accomplished when made intentionally in other localities.

Subcutaneous Injections. Phylacogen should be injected under the skin, not into the superficial fascia or into the muscle. Each injection should be made into a different area. The insertion of the deltoid muscle, the intrascapular region, under the abdominal skin, the thigh, etc., are localities where subcutaneous injections may be satisfactorily made.

Using our Special Phylacogen Syringe and a small and very sharp needle, the subcutaneous injection is no more difficult or painful than the ordinary hypodermatic injection of any medicament.

PACKAGE.

Phylacogens are marketed in amber glass vials of 10 Cc. capacity and of an improved style. The slender opening in the neck is

closed with a stopper, and the closed neck is then dipped in paraffin. This makes a hermetically sealed package. When using the Phylacogen, the operator or assistant removes the stopper, draws into the syringe the amount of Phylacogen desired, and replaces the stopper immediately, if less than the whole amount of 10 Cc. is to be given. Subsequent withdrawals of Phylacogen are made in the same manner. This plan enables the physician to administer such a dose as may be desired.

MIXED INFECTION PHYLACOGEN.

This is the Basic Phylacogen from which all the specific Phylacogens are prepared. Mixed infection is the foundation upon which the Phylacogen treatment is based—in other words, the theory of multiple infections.

Therapeutic Indications. Mixed Infection Phylacogen is indicated in all mixed infections, either acute or chronic, simple or grave, when the condition is not due to the preponderance of some specific micro-organism, the presence and effect of which has been demonstrated, as in typhoid fever, pneumonia, tuberculosis, erysipelas, gonorrhea, etc.; in such cases the indicated specific Phylacogen should be administered. Mixed Infection Phylacogen is indicated in all surgical infections, such as infected wounds or compound fractures, operation wounds, and infections following surgical

operations; also in fistulæ, abscesses, puerperal infection, appendicitis, peritonitis, otitis media, infected antra, carbuncle, infected glands, osteomyelitis, acute and chronic prostatitis (non-gonorrheal), pyosalpinx, pyelitis, mastitis, infected lateral sinus, gangrene, periostitis, septic phlebitis, phlegmon, and notably asthma and hay fever of bacterial etiology.

PNEUMONIA PHYLACOGEN.

Pneumonia Phylacogen is the specific Phylacogen indicated in the treatment of pneumonia. It is prepared by adding a definite volume of the filtrate from a pure culture of the Diplococcus pneumoniæ (Weichselbaum) to an equal volume of basic Mixed Infection Phylacogen.

Therapeutic Indications. Pneumonia Phylacogen is intended for the treatment of "pneumonia" and any other infections determined by the pneumococcus. In treating pneumococcus pulmonitis it should be understood that only the lung condition known as "pneumonia" will be relieved by Pneumonia Phylacogen; sequelæ, such as pleurisy with effusion, empyema and pulmonary abscess, will require the usual surgical intervention and drainage.

GONORRHEA PHYLACOGEN.

Gonorrhea Phylacogen is the specific Phylacogen indicated in the treatment of gonor-

rhea and its complications or sequelæ. It is prepared by adding a definite volume of the filtrate from a pure culture of the Micrococcus gonorrhœæ (Neisser) to an equal volume of basic Mixed Infection Phylacogen.

Therapeutic Indications. Gonorrhea Phylacogen is indicated in the treatment of any pathological condition due to infection with the Micrococcus gonorrhœæ. Dr. Schafer claims that Gonorrhea Phylacogen will relieve any case of true gonorrheal arthritis (and our clinical experience corroborates this); that most cases of acute or chronic rheumatism which do not show marked improvement after receiving six full doses of Rheumatism Phylacogen should be considered as gonorrheal and treated with Gonorrhea Phylacogen.

The complement fixation test for gonorrhea should be employed in all cases that do not promptly respond to the Rheumatism Phylacogen, for the purpose of determining the diagnosis. The complement deviation reaction for gonorrhea, when carried out with a polyvalent gonorrheal antigen, by the method recommended by Schwartz and McNeil and successfully employed by Gardner and Clowes, gives remarkably reliable results and permits of a specific differentiation even in the presence of syphilis and other diseases exhibiting complement deviation phenomena.

A majority of the cases reported as having

been treated with Gonorrhea Phylacogen have been cases of acute or chronic gonorrheal arthritis or so-called "rheumatism."

ERYSIPELAS PHYLACOGEN.

Erysipelas Phylacogen is the specific Phylacogen indicated in the treatment of erysipelas. It is prepared by mixing a definite volume of the filtrate obtained by treating the Streptococcus erysipelatis of Fehleisen, with an equal volume of the basic Mixed Infection Phylacogen.

Erysipelas Phylacogen has a record of upwards of 90 per cent. of cures in 272 cases in which it has been employed.

RHEUMATISM PHYLACOGEN.

Rheumatism Phylacogen is the specific Phylacogen indicated in the treatment of rheumatism. It is prepared by adding a definite volume of the filtrate from a pure culture of the Streptococcus rheumaticus to an equal volume of basic Mixed Infection Phylacogen.

A number of efforts to isolate and identify the specific micro-organism of rheumatism have been made. It would appear that Dagnino and Poynton and Paine have been successful, and, while many workers do not accept their conclusions, Meyer's studies seem to substantiate them. Walker and Beaton have

further confirmed the claims of Poynton and Paine, and have named the organism "Streptococcus Rheumaticus," to distinguish it from ordinary streptococci and to identify it as the specific organism causing rheumatism.

Therapeutic Indications. Rheumatism Phylacogen, as supplied by Parke, Davis & Company, is indicated in such conditions as are variously called "acute rheumatic fever," "acute articular rheumatism," "acute inflammatory rheumatism," and "chronic rheumatism," "rheumatic arthritis," "rheumatic myalgia," "rheumatic neuralgia," "rheumatic iritis," "lumbago," "sciatica," etc.—in other words, all pathologic conditions due to infection by the Streptococcus rheumaticus.

Clinical experiments would seem to warrant the conclusion that most cases of arthritis (not gonorrheal nor tubercular) may be successfully treated with Rheumatism Phylacogen (Schafer). In almost every instance the administration of Rheumatism Phylacogen, in the acute cases, has been followed by a relief from pain, disappearance of swelling and redness, and ability to freely move the affected joints.

In the chronic cases, the condition being the outcome of recurrent attacks of acute rheumatism, resulting in more or less immobility of the joints and attended by some swelling (with or without redness) and other evidences of inflammation, the administration of the Rheu-

matism Phylacogen has afforded prompt relief, the swelling and pain on motion disappearing with restoration of complete mobility. In chronic cases, in which the patient had not been suffering from an acute exacerbation, but complained of stiffness in the joints and pain on motion, with a history of previous attacks of rheumatism, equally good results have been obtained.

Questions of dosage, interval between doses, reactions, method of administration and other specific instructions as to treatment cannot be adequately described in the space at our disposal, but are fully treated in our literature on Phylacogen, which will be cheerfully sent to any physician requesting it.

TYPHOID PHYLACOGEN.

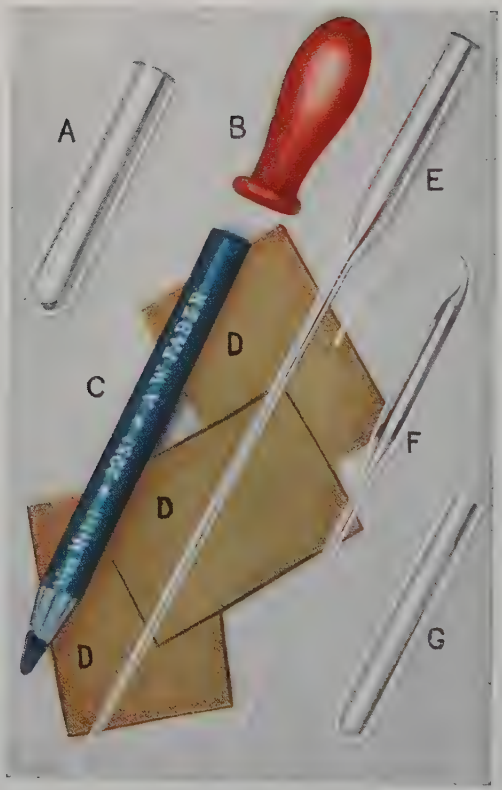
This preparation consists of a culture filtrate of the Bacillus typhosus, prepared in the same manner as all the other filtrates used in Phylacogen production, combined with an equal volume of the basic or Mixed Infection Phylacogen. The title indicates its uses. Reports have been made on the Phylacogen treatment of typhoid fever in 310 cases, with recovery in 283, or 91 per cent. A marked effect of the treatment in all favorable cases is the prompt subsidence of the fever and the early establishment of convalescence.

Dose. Typhoid Phylacogen should be ad-

ministered in beginning subcutaneous doses 1 to 2 Cc., gradually increased, one injection being given daily, or at intervals of twelve hours if temperature and other conditions permit. After the first dose, or at any time later, if it is found that the patient is not improving satisfactorily under hypodermatic treatment, the Phylacogen may be administered intravenously in the dose of $\frac{1}{8}$ Cc., very gradually increased up to 5 Cc.

For the technique and other particulars in regard to dosage the reader is referred to the chapter on Phylacogens in general and to our special literature on Typhoid Phylacogen which will be supplied on request.

Moro's Tuberculin Reaction, Second Degree.



THE OPSONIC OUTFIT.

A.—Blood Tube, 10 mm. (56 in box). B—Rubber Nipple (blind). C—Wax Pencil. D—Emery Paper (32 pieces). E—Opsonizing Pipette (56 in box). F—Blood Pipette (56 in box). G—Blood Tube, 6 mm. (56 in box).

Section 8.

TUBERCULINS.

Tuberculin may be defined as a product or products prepared from the tubercle bacterium, or the medium in which it has grown, of undertermined chemical nature but evidently protein in character, and which is capable of eliciting a specific reaction in animals infected with tuberculosis or sensitized by the products of the tubercle bacterium.

Both the diagnostic and therapeutic value of tuberculin are intimately associated with the "tuberculin reaction"—that is, the physiological response of the sensitized animal organism. The tuberculin reaction, as it is now understood, involves a dual phenomenon: first, the establishment of toxic manifestations (as evidenced by the general, local and focal reactions); and second, an immunizing response on the part of the injected subject. Our conception of the tuberculin reaction is based on the following general assumption. The active element in tuberculin, whether prepared artificially or elaborated by the organisms in their growth in the animal body, depends on a protein substance constituting a part of the bacterial cell, this protein being relatively nontoxic to the normal animal, but producing

marked reaction in the presence of tubercular infection. The active constituents of tuberculin preparations are considered as differing quantitatively but being qualitatively the same, and the specific reaction to be due to the tubercle protein and to follow the general laws of protein sensitization. The reaction of the sensitized subject to the injection of tuberculin is ascribed to the splitting up of the tuberculin by specific lysins formed as the result of the stimulation afforded by the escape of analogous material at the focus of infection. The metabolic products set free by these lysins, if not excessive, stimulate the tissues of the host to the elaboration of specific antibodies. Thus the tuberculin reaction involves both toxic and immunizing phenomena. The absence of the specific lysin required to split up the bacillary protein, explains our failure to elicit the characteristic tuberculin reaction in non-infected individuals.

Clinically, the tuberculin reaction is characterized by general, local and focal manifestations. The following description is quoted from Klebs' text-book on "Tuberculosis:"

Typical Reaction. In a typical tuberculin reaction, usually ten to eighteen hours after the injection the patient begins to feel feverish (possibly chilly at first), heavy and dull, experiences lassitude and has slight elevation of temperature, often detected in the urine stream or rectum before it is detected in the mouth. These symptoms are rapidly aggravated, and in a short time the patient feels so ill that he is forced to go to bed, with pains in the back, legs and head, which are often severe. The tendency to cough may be in-

creased, oppression may be felt in the chest, and the expectoration may be increased. The temperature may rise to 103 F.° or higher, the pulse-rate reach 120 or over, the urine may be increased, with a slight trace of albumen or a diazo-reaction, and, on the whole, the patient is ill. These symptoms persist for eight to twelve hours, and usually on the following day the patient feels a little weak but otherwise all right. In a few instances the reaction is delayed for forty-eight hours, and in others the rise of temperature is less (100°F.) but persists for several days, while the symptoms may be very severe.

Skin Reaction. The classical signs of inflammation occur at the point of injection and persist for one or two days, but, except with B. E., never go on to suppuration if asepsis has been preserved. Sites of former injections frequently present the same signs, though less pronounced, and the conjunctiva, if the ophthalmic test has been given, as well as the perceptible tuberculous foci, all show signs of more or less marked hyperemia. The recent work of von Pirquet ('07), Wolff-Eisner ('08), Calmette ('07), and others on the reactions occurring in the skin and in the eye, following the application of tuberculin to these parts, suggests that this local reaction is definitely connected with the tuberculin and not due, especially when great dilutions are used, to any local irritation either by the tuberculin, by the glycerin, or by other constituents or diluents. In many instances when this local reaction is disregarded and the usual rate of increase followed, the skin reaction becomes more pronounced and finally is accompanied by a general reaction.

The relative irritability of the skin of different areas has not been definitely worked out, nor as yet is this reaction satisfactorily explained, though many attribute it to increased susceptibility (allergie, anaphylaxis). It is much less pronounced when the injection is made in the back than when given in the limbs. For the purpose of forestalling a general reaction, it would seem advisable to give the tuberculin in the forearm, an area of skin of great sensitiveness, a procedure which Spengler has long followed. Injection of tuberculin in the skin causes very painful redness and swelling, and at times minute quantities of tuberculin may accidentally be deposited in the skin on withdrawal of the needle.

These "skin" reactions occur in different individuals with different intensity and vary at different times in the same individual. They occur more frequently at first in some patients, and in others are never present or only with large concentrated doses. They are directly connected with the form of tuberculin used, B. E. causing the reaction most frequently even in great dilution (0.00001 mg.). In this connection it is of interest to note that patients who have received

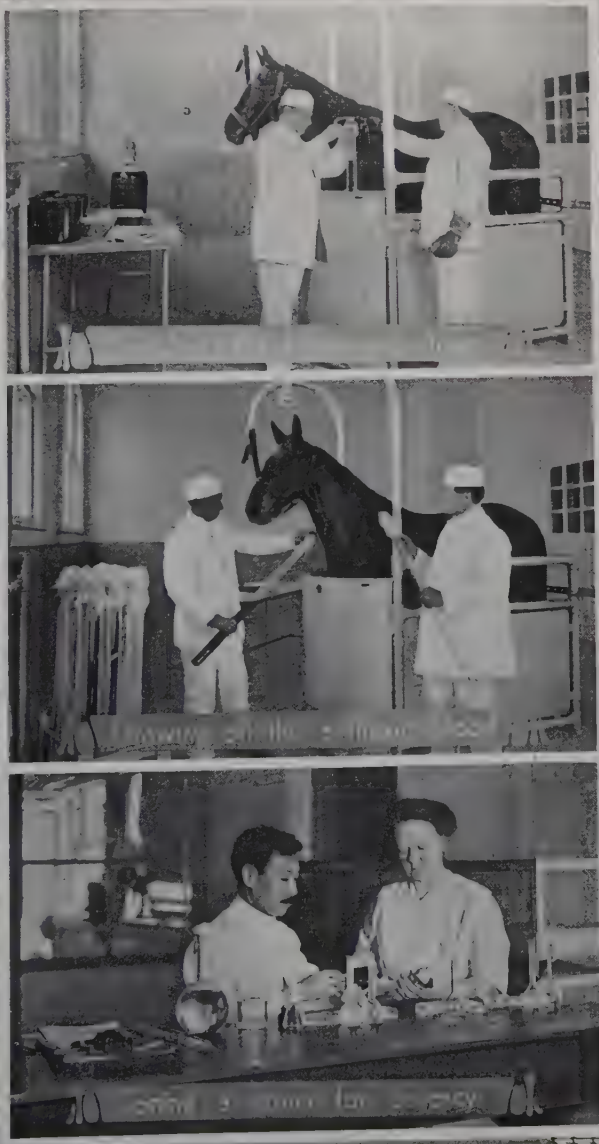
the ophthalmo-tuberculin test and either reacted or failed to react (solution used 1:200), in some instances react again more severely or for the first time after the subcutaneous injection of tuberculin. This may occur after tuberculin is used in therapeutic doses and is one of the objections to the ophthalmo-tuberculin test.

Tuberculin should always be administered in the same region of the body, but on alternate sides. The concentration of the dose, on the whole, seems to have some influence on the "skin" reaction, and a few patients do react in this way to large doses of concentrated tuberculin, particularly B. E., but the majority take 1 Cc. undiluted of O. T. or B. F. with very slight reaction. The injection of tuberculin into an area of induration produced by a former injection is much more likely to cause this reaction, and in the case of B. E. may produce sterile abscesses. Whenever this "skin" reaction occurs it is well to repeat the dose or to advance very cautiously, for in some cases it is undoubtedly the forerunner of a general reaction. A very severe "skin" reaction would indicate omission of one or two doses and the use of smaller doses for a time.

Organ Reactions. The occurrence of local or "organ" reactions, manifested by hyperemia, are of great value when they so occur that they can be observed readily (*e. g.* in lupus, laryngitis, etc.,) but it is fallacious to base any method of dosage on the "organ reaction" occurring in the lungs, for it cannot be detected by our methods of exploration in at least sixty per cent. of all tuberculin reactions where severe general reactions occur, and, further, the occurrence of physical signs in the lungs is notoriously uncertain even when tuberculin is not administered. Petruschky holds these organ reactions of importance for cure, and Phillipi lays considerable stress on the increase and decrease of catarrhal signs.

TUBERCULIN PREPARATIONS.

Ever since Koch's first report on tuberculin, ceaseless experimentation has been carried out in attempts to accomplish the production of an ideal tuberculin. As has already been pointed out, the active constituent in all tuberculins is apparently the same, so that work along this line practically resolves itself into an endeavor to eliminate impurities from the tuberculin.



Success in tuberculin therapy depends largely upon the physician's familiarity with the tuberculin which he is using, and not upon special virtues to be attributed to any particular preparation. It is infinitely better for the tuberculin therapist to have an intimate knowledge of one preparation, than a smattering knowledge of half a dozen. From the multitude of preparations which have been developed, the following stand out as the ones most commonly used and universally accepted.

Old Tuberculin, Koch (O. T.). Tuberculin Old represents a pure culture of Bacterium tuberculosis, grown on 5-per-cent. glycerin bouillon, evaporated over a steam bath to one-tenth of its original volume, and filtered. It contains all the soluble products of the tubercle bacterium in 50-per-cent. glycerin solution. In addition to its use as such, Tuberculin Old is employed as the basis of the Tuberculin Ointment (see Moro Test), and, after purification by alcoholic precipitation, for the preparation of Tuberculn Discs (see Ophthalmic Test).

Tuberculin Residue, Koch (T. R.). In the preparation of Tuberculin T. R., the water-soluble constituents are removed, the non-water-soluble material only being employed. A virulent culture of Bacterium tuberculosis is dried, the desiccated material finely pulverized by long continued grinding in a ball

mill, treated with physiologic salt solution, and the supernatant solution containing the water-soluble material is discarded. The residue is ground with 20-per-cent. glycerin and standardized to contain a definite amount of solids per Cc.

Bacillen Emulsion, Koch (*B. E.*). The Bacillen Emulsion, like Tuberculin T. R., is prepared from the bacterial body. The well-washed, living, virulent tubercle organisms are thoroughly dried and ground in the porcelain ball mill for several weeks. The ground material is then thoroughly emulsified with 50-per-cent. glycerin and standardized to a definite amount of solids per Cc.

Bouillon Filtrate, Denys (*B. F.*). This product represents the unheated filtrate from a bouillon culture of Bacterium tuberculosis. It is filtered first through paper and then through porcelain (Berkefeld) filters, and contains all the soluble products of the organism as it grows in a bouillon medium.

STANDARDIZATION OF TUBERCULIN.

As prepared by Koch, Tuberculin T. R. represented 2 milligrams of solids to the cubic centimeter, and Tuberculin B. E. 5 milligrams of solids to the cubic centimeter. In order to eliminate confusion, to make these products uniform in strength, and facilitate the preparation of dilutions, Parke, Davis & Co. put up

both T. R. and B. E. in the strength of 1 milligram to the cubic centimeter. As the dose of these products is never expressed in liquid measure, this should not cause any confusion or misunderstanding, and on the other hand it simplifies greatly the problem of making dilutions. Tuberculin Old and Tuberculin B. F. being filtrate products, it is impossible to standardize them excepting in so far as this may be accomplished by uniform methods of production. The term "milligram," as applied to the dosage of these filtrate products, is to be interpreted as meaning cubic millimeter.

TUBERCULIN IN DIAGNOSIS.

Aside from the general principles of tuberculin sensitization which have already been discussed in considering the tuberculin reaction, the application of the diagnostic tests is modified by certain factors associated with the clinical condition of the patient. A patient suffering from active tuberculosis reacts markedly to the tuberculin test because the body cells readily respond to the injection, and the tuberculin protein is split up with great rapidity. A patient with an active tuberculosis and lowered vitality reacts more moderately because the organism is less capable of responding to the specific stimulation. Advanced cases of active tuberculosis may give

little or no reaction because the immunizing mechanism of the patient has been exhausted. Since such cases present no difficulties from a diagnostic standpoint, this fact does not vitiate the value of the tuberculin test. A quiescent lesion usually gives a weak reaction, and healed lesions may react weakly for a long time, possibly as a result of the specific lysins remaining attached to certain body cells. The tuberculin tests in common use are the *subcutaneous* (Koch), *cutaneous* (von Pirquet), *percutaneous* (Moro), *intracutaneous* (Mantoux), and *ophthalmic* (Wolff-Eisner and Calmette).

Subcutaneous Test. The value of the subcutaneous test depends upon certain definite phenomena following the injection of Tuberculin Old in doses of from 0.1 to 10 milligrams, Koch having established 10 milligrams as the dose of Tuberculin Old which can be administered to a healthy individual without producing the characteristic symptoms. Various schemata for giving these doses have been presented, but do not seem to offer any improvement over the original suggestion of Koch (three doses, of 1, 5, and finally 10 milligrams, given three days apart), excepting that it is now believed advisable to begin with 0.1 milligram. The constitutional symptoms attending a positive reaction are: rise in temperature, general lassitude, heaviness in

the limbs, and pain or discomfort in the head and back. The rise in temperature usually develops within eight to sixteen hours, sometimes as early as three to four hours, occasionally after several days, usually returning to normal within twenty-four to forty-eight hours. The subcutaneous test is not used extensively in human practice at the present time, owing to the apprehension of severe reaction with sloughing at the focus of infection and the possible dissemination of the infective material.

Cutaneous Test. The von Pirquet test consists of the application of Tuberculin Old to cutaneous scarifications made by means of a von Pirquet rotary scarifier. An areola of inflammation surrounds the site of inoculation. Control scarifications to which the tuberculin is not applied afford a comparison of the specific reaction to such irritation as results from the trauma. In active tuberculosis the reaction usually develops within twenty-four hours. In healed or latent lesions it more commonly develops after a couple of days.

Von Pirquet published the following directions for making the test in the *Journal of the American Medical Association*, Feb. 27, 1909, page 675:

My method of applying the test is as follows: The skin of the forearm is scrubbed with ether, then two drops of undiluted Old

Tuberculin are dropped about four inches distant from each other. Then, with a vaccinating lancet, the point of which has the form of a small chisel, a superficial circular scarification is made between the two drops (for the control of the traumatic redness following the small scarification). Finally, the same scarification is made inside of the two drops. A few fibres of cotton are put on the drops so that they will not flow. After five minutes the cotton is taken off. No dressing is applied. The papule is examined after twenty-four and forty-eight hours. It is considered as positive when the tuberculin scarifications are clearly different from the control, but the inflammatory reactive area must measure at least one-fifth of an inch (5 mm.)

Preliminary: Cleanse the site chosen with *soap* and *water*, and carefully dry.

Take the small rubber bulb in the left hand, with the neck of the bulb pointing to the right. One of the sealed glass tubes, held in the right hand, is inserted into the opening in the neck or cup-shaped end of the bulb and, with slightly rotary motion, pushed through until the bulb is impaled upon and resting at about the center of the tube. The end of the tube to the left is then broken off and the tube drawn back until the open end is well within the cavity of the bulb. Now break off the other (right) end of the tube. The tuberculin may be expelled by closing the air hole in the rubber bulb with the finger and applying pressure.

The site chosen may conveniently be the inner side of the arm, since in this region there are few hairs and the skin is soft and tender.

No other disinfectant should be used than ether; watery antiseptics and alcohol cause the tuberculin to flow.

The scarifier used by von Pirquet is a chisel-shaped point about 1/16 inch in width. It is held at right angles to the skin and rotated. The amount of abrasion should be such that the control spot shows a scab the next day, but blood should not be drawn.

The amount of cotton should be sufficient to hold the tuberculin in contact with the scarified area, but not enough to absorb it.

The following suggestions are taken from an article by von Pirquet, found in the "*Handbuch der Technik und Methodik der Immunitatsforschung*," von Kraus und Levaditi, Jena, 1908, Vol. 1, page 1035:

The vaccination spot and the control spot at first exhibit the same appearance as a result of the trauma. This consists of a small wheal formed in a few minutes after the application of the instrument, followed by a delicate rosy halo which disappears in a few hours. On the small, slightly raised reddish spot a scab forms as large as a pinhead, which may remain for one or more weeks. The intensity of this traumatic reaction varies with the depth of the scarification and with the individual differences in the skin.

Many times the control spot gives a typically positive reaction, but only when near a vaccination spot reacting positively; never with negative cases, also never when the control spot is prepared separately. The reaction in such cases is due to the extension of the tuberculin upon the control spot.

The Positive Reaction. The positive reaction may develop quite quickly (after a few hours) as a reddish zone surrounding the scarified area. The duration of the latent period may vary between three hours and several days; in most cases, however, development is complete in twenty-four hours. Reactions are designated as "sluggish" when the latent period is more than twenty-four hours, and such instances are more often found with older children, especially with clinically unsuspected cases. Children obviously tubercular show the "sluggish" reaction only exceptionally.

The specific reaction begins normally as a slightly raised red spot

spreading from the scarification outward and quickly increasing in extent and height. The diameter of the papule may reach 30 mm. (1⅕ inches), but is usually about 10 mm. (2/5 inch).

Only exceptionally is the center soft and vesicle-like, and pus is never formed. In color, great variation may be observed. In general, strong men with skin of a healthy color show a highly red papule, anemic individuals a pale red reaction. Many times the hyperemia is entirely absent, so that the papule is recognized only through the sense of touch or by lateral illumination. Colorless papules or white spots without exudation are found often in the late stages of tuberculosis, and indicate the inability of the skin to react.

Description of the Papule. The boundary of the papule is sometimes round, sometimes jagged; occasionally long spurs are seen along the path of the lymph vessels. Often the edge of the papule is formed of small ill-defined follicle-like swellings. When such little knob-like swellings are seen in the immediate region of the papule, the reaction is termed "scrofulous," since this form is found chiefly with scrofulous children and reminds one of lichen scrofulosus.

The hyperemia usually does not extend beyond the borders of the exudation. With an intensive reaction, however, there may be seen many times a rose-red halo surrounding the papule, not unlike that seen in smallpox vaccination.

The maximum, both in extent and height of the inflammatory area, is usually attained in forty-eight hours after vaccination. Exudation then diminishes, the red color disappears, playing into violet and yellow, and gradually passing into a pigment which may remain for a week. The swelling is lost to the sense of touch in from five to eight days. A ready scaling of the epidermis follows.

The younger the children, the more quickly absorbed are the remains of the inflammatory process. This may be completed in three days with infants. If the patient can be seen but once, the best time is forty-eight hours after vaccination.

Revaccination. A revaccination may exhibit a positive reaction where a negative result follows the first trial.

Percutaneous Test. The Moro test consists of the application to the skin of Tuberculin Old incorporated in lanolin. Plain lanolin may be applied to a corresponding area as control.

Dr. Moro published the following directions

for making the test in the *New York and Philadelphia Medical Journal*, June 27, 1908, page 1233:

I rub into the skin of the chest or abdomen, over an area of 4 square inches, a piece of the following ointment of the size of a pea, for about half a minute, and permit the ointment to remain on the surface of the skin and to spontaneously absorb. The effect of this inunction is observed on the following day or later, observation being usually best on the second day.

The ointment is prescribed thus:

R Koch's old tuberculin. . . .5 Cc.
Anhydrous wool fat . . . .5 Gm.

The result is positive when small papules appear over the area of the inunction or in its immediate vicinity, negative when the skin shows no changes of any kind. With the positive reaction one often observes only a few very pale papules. Occasionally the papules are very numerous and red, and only exceptionally the skin in the region of the inunction is very much reddened and itches. The papules usually disappear at the end of a week. Other local or general symptoms have not been observed.

In the *Muench. Med. Woch.* article of February 4, 1908, three grades of the positive reaction are distinguished, as follows:

(1) *Weak Reaction.* On the test area appear, in from 24 to 48 hours, seldom later, from 2 to 10 nodules which are entirely distinct and for the most part markedly red, though rarely they may be indistinctly pale, and having a diameter of 1 to 2 mm. Usually this eruption disappears after a few days without even causing any itching.

(2) *Moderately Strong Reaction.* On the test area there appears, usually in the course of the first 24 hours, a very large number, up to 100 or more, of red nodules which may be miliary in size or they may have a diameter of as much as 3 mm. The skin in the region of the eruption is decidedly red and the reaction is confined to the spot of inunction, being accompanied at first by slight itching. This appearance remains several days unchanged and fades out gradually.

(3) *Strong Reaction.* On the test area there appear after a few hours, in most cases, a very large number, 100 or more, of large red nodules with an inflamed background. The dermatitis is always accompanied with itching. Many of the eruptions form an exudate and may reach a diameter of 5 to 8 mm. (0.2 to 0.3 inch). They are

not confined to the point of application, but extend to the immediate vicinity. After a few days the papular eruption dries up and becomes scaly After two weeks, outside of a brownish pigmentation there is nothing to be noticed on the skin.

CONFIRMATORY EXPERIMENTS.

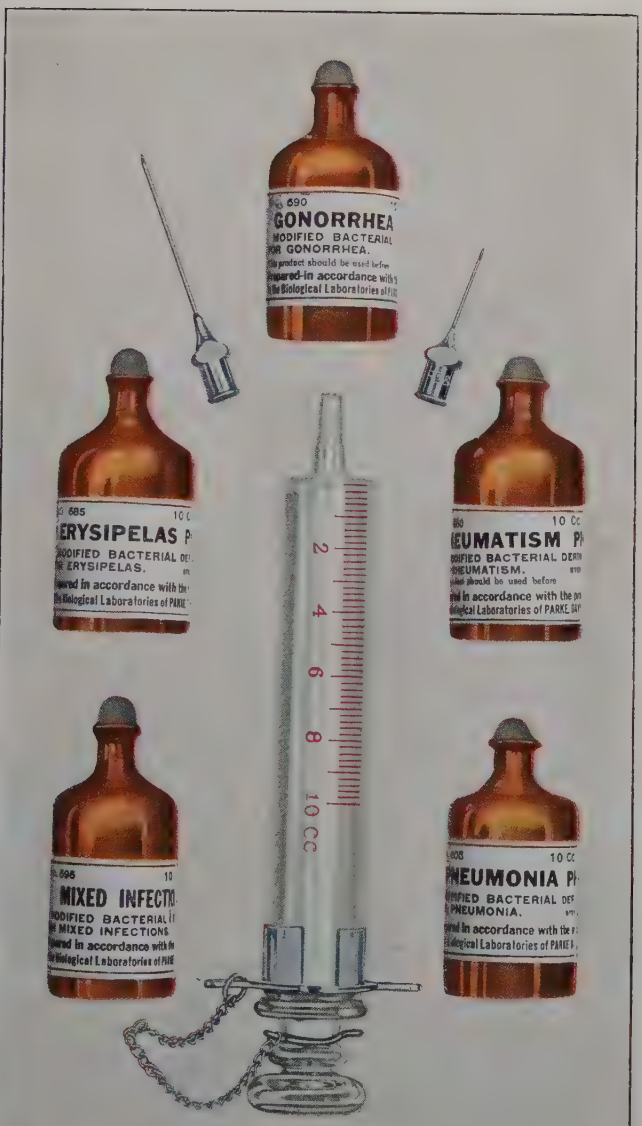
Heinemann (*Muench. Med. Wochenschrift*, 1908, No. 11, p. 556) confirmed the Moro test with adults, and, as a result of investigations including 66 cases tested side by side with the conjunctival reaction and 108 cases in which the ointment was the only skin test applied, concludes that with adults the Moro ointment test as a diagnostic measure is at least as valuable as the Calmette test.

Hamill, Carpenter, and Cope (*Archives of Internal Medicine*, Vol. 2, 1908-1909, p. 405) tested the conjunctival (Calmette), the scarification (von Pirquet), and the ointment (Moro) reactions on 132 cases, of which 122 reacted positively. The authors conclude that there was almost absolute uniformity as to the reaction with these three tests.

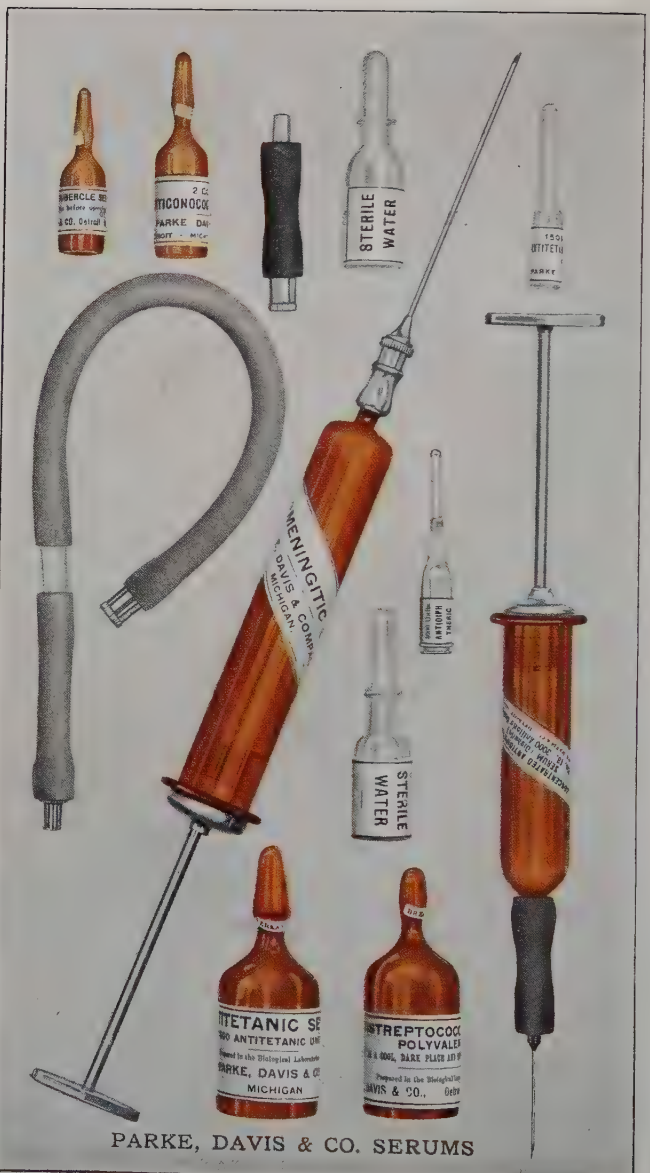
Moro (*Beitrage zur Klinik der Tuberculose*, Vol. 12, 1909, p. 207) used his test upon 388 children, with the von Pirquet reaction as a control, from which he concludes that the ointment test gives results almost exactly parallel with those of the scarification test.

CONSENSUS OF OPINION.

While all observers are not agreed as to the exact value of this reaction, the consensus of



PARKE, DAVIS & CO. PHYLACOGENS



PARKE, DAVIS & CO. SERUMS

recent opinion is perhaps expressed by the following conclusions of Dr. Henry S. Patterson, of New York (*Archives of Internal Medicine*, Vol. 3, 1909, p. 299), based upon a review of the literature and 171 of his own cases in which the von Pirquet reaction was used as a comparison:

"(1) The Moro test is absolutely harmless and simple to use.

"(2) It is better adapted to use among adults than the von Pirquet test, because it does not produce a reaction so frequently among those clinically free from tuberculosis.

"(3) It produces a reaction probably as frequently as the ocular reaction in the tuberculous and in the clinically free cases, but is devoid of the danger incident to the conjunctival test."

On the other hand a negative reaction with the Moro test is by no means absolute evidence of the absence of a tuberculous condition and cannot be relied upon with the same confidence as a negative von Pirquet.

Intracutaneous Test. The intracutaneous test consists of the injection of Tuberculin Old intradermally, a nodular area of inflammation following its application in positive cases. The scope of this test is comparable to the von Pirquet, but as the technique is somewhat more difficult it has been less extensively employed.

Ophthalmic Test. Wolff-Eisner and Calmette were the first to report that a drop of 10-per-cent. tuberculin, placed in the eye of a tuberculous patient, produced a characteristic reddening of the conjunctiva, but not when placed in the eye of a person free from tuberculosis.

PREPARATION OF TUBERCULIN DISCS.

The tuberculin is purified by precipitating the active constituents with alcohol and thoroughly washing the precipitate. The precipitate is then dried and made up into discs, each containing 3.3 mg. (0.0033 Gm.). Hence, one disc dissolved in .33 Cc. (5 minims) of sterile distilled water makes a 1-per-cent. solution. The disc and the water may be placed in a small conical graduate or a spoon, and the solution of the tuberculin will be hastened by drawing the liquid up and down in the eye-dropper. *The dilution should be used as soon as made.*

HOW TO MAKE THE OPHTHALMIC TEST.

To make the test, instill one drop of the 1-per-cent. solution into one eye of the patient. The other eye then serves as a normal control by which to judge of the changes in the tested eye.

The reaction which occurs in the eye of a tuberculous patient is manifested by redness

of the caruncle spreading to the conjunctiva, by lacrimation, by a fibrinous exudate on the caruncle, by chemosis, and by some discomfort. These symptoms may vary in severity from the mildest of manifestations to a very severe inflammation, with photophobia and considerable interference with vision owing to the swelling and the increased secretions. The subjective symptoms are usually much less marked than would be expected from the appearances.

WHEN THE REACTION APPEARS.

The reaction usually begins to become manifest three to ten hours after applying the tuberculin, is at its height in from six to twelve hours, and disappears in from twenty-four to thirty-six hours.

In some cases the reaction is late in appearing (twelve to twenty-four hours) and may persist several days before clearing up.

TO REPEAT THE TEST.

In repeating the test on the same patient the other eye should be utilized, because one application of tuberculin has a tendency to so sensitize that eye that a second application to the same eye, made after the lapse of a suitable interval (ten days to two weeks), is liable to be followed by a reaction, even in a non-tuberculous patient.

FACTS RESPECTING THE REACTION.

Patients in advanced stages of tuberculosis frequently do not give the ophthalmic reaction, probably for the same reason that they do not react to the subcutaneous exhibition of tuberculin.

The ophthalmo reaction does not produce immunity, but the same patient will react to a subsequent ophthalmic test in the other eye, to a cutaneous test or to a subcutaneous injection of tuberculin.

PRECAUTIONS NECESSARY.

Although the ophthalmo-tuberculin test has been used in many hundreds of cases without producing deleterious effects, it is proper to note that in a few instances so severe a reaction has developed as to endanger the eye, especially when there was already a diseased condition present.

TUBERCULIN IN TREATMENT.

The first principle to be fixed in mind in considering tuberculin therapy is that it is nothing new to the patient. Every patient suffering from a tubercular infection treats himself with tuberculin escaping from the focus of infection. Tuberculin therapy aims to reinforce nature's attempts at immuniza-

tion, to spur the body cells to a greater antibody-formation by increasing the specific stimulus. It is not offered as a substitute for proper dietetic and hygienic measures, but is expected to act in conjunction with other recognized lines of treatment.

Dosage. In the therapeutic use of tuberculin the question of dosage is probably the most important one which is to be considered. Denys, Trudeau, Sahli, Brown, Baldwin, and a majority of the other well-known authorities advise the use of a very small initial dose, and the carrying of the treatment by gradually increasing doses to as high a degree of tuberculin tolerance as can be accomplished without the production of marked reaction. The initial dose most commonly employed is 0.00000001 Gm. (1/100,000 milligram). In cases with considerable febrile disturbance even smaller doses are sometimes used.

In this connection attention is directed to the following quotation from Volume I, Osler-McCrea, last edition of Modern Medicine (second edition, 1913):

"*Dosage and Interval.* In the proper selection of the dose and of the interval between doses lies the key to the successful treatment. Tuberculin should be looked upon as a most powerful poison, capable of producing irreparable harm in ignorant or careless hands. The slightest departure from the ordinary

course of events should be thoughtfully considered. Tolerance of the tubercle toxin varies greatly (from 1 to 10,000, Sahli) and apparently is independent of sex, of amount of pulmonary involvement, and of general physique.

"The beginning dose should always be far below that expected to excite reaction. In febrile patients and in those who have been subjected to the tuberculin test, it should be smaller than in others. With B. E., Koch's beginning dose of 0.0000025 Gm. should be reduced to 0.000001 Gm. (1/1,000,000 milligram) for afebrile and to 0.0000001 (1/10,000,000 milligram) for febrile patients. This is also the dose of T. R. For B. F. or O. T., the usual beginning dose may be 5/10,000,000 or 10/10,000,000 Cc., though in a few cases, especially if febrile, it may be 1/10,000,000 or 1/100,000,000 Cc."

DIRECTIONS FOR MAKING DILUTIONS OF TUBERCULIN T. R. AND B. E.

Make up the dilutions as required. They will not keep.

The following table may be helpful to those not accustomed to making the dilutions specified. The dilutions are best made with sterile physiologic salt solution containing 0.5 per cent. carbolic acid, which may be made as follows: Salt, 8.5; carbolic acid, 5; water, to make 1000.

1 Cc. Tuberculin B.E. or T.R. represents 1 milligram of solid material. .Sol. 0.

	Dilution	Am't of Tubercle Solids per Cc.	
0.1 Cc. Sol. 0 + 0.9 Cc. diluent, or 1 Cc. Sol. 0 + 9 Cc. diluent	= 1:10	0.1 Mg.	Sol. I.
1 Cc. Sol. I + 9 Cc. diluent	= 1:100	0.01 Mg.	Sol. II.
1 Cc. Sol. II + 9 Cc. diluent	= 1:1000	0.001 Mg.	Sol. III.
1 Cc. Sol. III + 9 Cc. diluent	= 1:10,000	0.0001 Mg.	Sol. IV.
1 Cc. Sol. IV + 9 Cc. diluent	= 1:100,000	0.00001 Mg.	Sol. V.
1 Cc. Sol. V + 9 Cc. diluent	= 1:1,000,000	0.000001 Mg.	Sol. VI.

TABLE II.—SHOWING THE AMOUNT OF TUBERCLE SOLID SUBSTANCE (DRY) IN VARYING AMOUNTS OF THE DIFFERENT DILUTIONS OF T. R. CONCENTRATED AND B. E.

Size of Dose.	Dilutions (*see above*).					
	Sol. VI. 1:1,000,000	Sol. V. 1:100,000	Sol. IV. 1:10,000	Sol. III. 1:1000	Sol. II. 1:100	Sol. I 1:10
	Mg.	Mg.	Mg.	Mg.	Mg.	Mg.
0.1 Cc. contains	.0000001	.000001	.00001	.0001	.001	.01
.2 " "	.0000002	.000002	.00002	.0002	.002	.02
.3 " "	.0000003	.000003	.00003	.0003	.003	.03
.4 " "	.0000004	.000004	.00004	.0004	.004	.04
.5 " "	.0000005	.000005	.00005	.0005	.005	.05
.6 " "	.0000006	.000006	.00006	.0006	.006	.06
.7 " "	.0000007	.000007	.00007	.0007	.007	.07
.8 " "	.0000008	.000008	.00008	.0008	.008	.08
.9 " "	.0000009	.000009	.00009	.0009	.009	.09
1.0 " "	.0000010	.000010	.00010	.0010	.010	.10
1 minim "	.00000006	.0000006	.000006	.00006	.0006	.006
2 minims "	.00000012	.0000012	.000012	.00012	.0012	.012
3 " "	.00000018	.0000018	.000018	.00018	.0018	.018
4 " "	.00000025	.0000025	.000025	.00025	.0025	.025
5 " "	.00000031	.0000031	.000031	.00031	.0031	.031
6 " "	.00000037	.0000037	.000037	.00037	.0037	.037
7 " "	.00000043	.0000043	.000043	.00043	.0043	.043
8 " "	.00000049	.0000049	.000049	.00049	.0049	.049
9 " "	.00000055	.0000055	.000055	.00055	.0055	.055
10 " "	.00000062	.0000062	.000062	.00062	.0062	.062
11 " "	.00000068	.0000068	.000068	.00068	.0068	.068
12 " "	.00000074	.0000074	.000074	.00074	.0074	.074
13 " "	.00000080	.0000080	.000080	.00080	.0080	.080
14 " "	.00000086	.0000086	.000086	.00086	.0086	.086
15 " "	.00000093	.0000093	.000093	.00093	.0093	.093
16 " "	.00000100	.0000100	.000100	.00100	.0100	.100

These tables do not provide the reader with accurately graded serial doses, based on a defi-

nite percentage of increase from dose to dose. but with their aid such serial dilutions can be worked out. The whole matter is greatly simplified by the Tuberculin Tablets described on page 149.

TUBERCULIN T. R. (DILUTE).

This differs in strength from Tuberculin T. R. (Concentrated). One cubic centimeter contains one one-thousandth of a milligram of dry tubercle solids. In its preparation the refined residue is brought into solution in a mixture of glycerin and water and diluted with physiologic salt solution containing 0.2-per-cent. trikresol.

Dosage. Measured in units of tubercle solids, the dose is the same as that of T. R. concentrated.

	Approximately.	Exactly.
1 minim of Tuberculin T. R. (Dilute) contains	1-16200Mg.	1-16230 Mg.
2 minims contains	1-8100 "	1-8115 "
3 " "	1-5400 "	1-5410 "
4 " "	1-4050 "	1-4058 "
5 " "	1-3250 "	1-3246 "
6 " "	1-2700 "	1-2705 "
7 " "	1-2320 "	1-2319 "
8 " "	1-2030 "	1-2029 "
9 " "	1-1800 "	1-1803 "
10 " "	1-1625 "	1-1623 "
11 " "	1-1475 "	1-1476 "
12 " "	1-1350 "	1-1353 "
13 " "	1-1250 "	1-1248 "
14 " "	1-1160 "	1-1159 "
15 " "	1-1080 "	1-1082 "
16 " "	1-1015 "	1-1014 "
17 " "	1-950 "	1-955 "
18 " "	1-900 "	1-902 "
19 " "	1-850 "	1-852 "
20 " "	1-810 "	1-812 "
21 " "	1-775 "	1-773 "

	Approximately.	Exactly.
22 minims contains	1-740 Mg.	1-738 Mg.
23 " "	1-700 "	1-706 "
24 " "	1-675 "	1-676 "
25 " "	1-650 "	1-649 "
26 " "	1-625 "	1-624 "
27 " "	1-600 "	1-601 "
28 " "	1-580 "	1-580 "
29 " "	1-560 "	1-560 "
30 " "	1-540 "	1-540 "
31 " "	1-525 "	1-525 "
32 " "	1-500 "	1-500 "

TABLETS OF TUBERCULIN (FOR HYPODERMATIC USE).

T. R. (Tuberculin Residue); and B. E. (Bacillary Emulsion).

The preparation of accurate serial dilutions of the Tuberculins has always been a source of much annoyance and inconvenience to the busy physician. In order to overcome this, Parke, Davis & Co. have perfected a method by which it is now possible to prepare dry Tuberculins made up into soluble hypodermatic tablets of unvarying content. The two most generally used Tuberculins are the T. R. (Tuberculin Residue) and the B. E. (Bacillary Emulsion), and these are the ones we have selected and put in the tablet form.

THE PREPARATION OF TABLETS OF TUBERCULIN T. R.

In making Tablets Tuberculin T. R., the mass culture is washed repeatedly, agitated again in water, washed, ground to complete disintegration, and dried. Instead of bringing the dried sediment into a suspension with

glycerin and water, it is thoroughly mixed with a suitable base, similar to that employed for the ordinary hypodermatic tablet, and is diluted with this base so that each tablet represents a definite amount of the dry tubercle solids.

THE PREPARATION OF TABLETS OF TUBERCULIN B. E.

In making Tablets Tuberculin, B. E., the material is prepared, with one modification, exactly as the liquid B. E. Instead of bringing the dried sediment into an emulsion with glycerin, it is thoroughly mixed with a suitable base, similar to that employed for the ordinary hypodermatic tablet, and is diluted with this base so that each tablet represents a definite amount of the dry Tuberculin.

TABLETS MORE CONVENIENT AND MORE STABLE THAN SOLUTIONS.

The advantage of dispensing Tuberculins in tablets over the original method of putting them out cannot be overestimated. In tablet form Tuberculin is more stable, is in a more convenient form for the physician, and dilutions can be prepared with a minimum degree of manipulation, either in the hypodermatic syringe or by means of a small graduate. It has been known for several years that Tuberculin in liquid form, especially in high dilutions, deteriorates rapidly, and for that reason

the practice of dispensing the product in ready-made dilutions has not appealed to the great majority of thinking physicians. In tablet form Tuberculin can be dispensed in a highly diluted form with the assurance that its strength and keeping property have not been impaired. For use at the bedside or in office practice Tuberculin tablets are ideal, and for institutional work they are also a great convenience.

THE QUESTION OF DOSE.

In the use of Tuberculin Tablets the same principles of dosage as have already been discussed apply.

HOW THE DOSES SHOULD BE INCREASED.

It is of the greatest importance that the therapeutist proceed with caution in increasing the dosage, and it is upon this point that the success or failure of tuberculin therapy often depends. Attempts to increase the dose by a definite quantity of a certain solution (for instance, 1/10 Cc.) have not been satisfactory, because this does not accomplish a uniform degree of increase. In other words, if treatment is begun with 0.1 Cc. of 1:100,000 solution, and the dose is increased by 0.1 Cc. of the solution at each injection, the first increase is 100 per cent., the second 50 per cent., the third only 33.3 per cent. The advisability, therefore, of adopting a system of dosage

which affords a uniform percentage of increase is at once apparent, and the scale which has been worked out on a logarithmic basis (see Tables III and IV) is, perhaps, the best solution of this problem.

DIRECTIONS FOR USE.

Two methods of preparing the dilutions may be employed: the Syringe Method and the Graduate Method. Either is relatively simple, but when the ordinary hypodermatic syringe is used for the injections the Graduate Method is more accurate.

In using the Syringe Method, the tablet is dissolved in a 1-Cc. graduated syringe, and the dose is controlled by the amount of solution injected. For this purpose, an accurately graduated syringe is a necessity. A special Tuberculin syringe has been designed by Dr. Fornier which can be recommended for making the serial dilutions with great convenience and relative accuracy. This syringe is accurately graduated in hundredths of a cubic centimeter.

The initial dose, .00001 (1/100,000) mg., is represented by 0.1 Cc. of a solution prepared by dissolving a 1-10000 tablet in 1 Cc. This is increased with each injection, the amount depending upon which of the columns of the scale is followed, or, in other words, upon how rapidly the physician desires to increase the dose.

When the amount has been increased to 1 Cc. of this solution, treatment is continued with next strength tablet, beginning as before with 0.1 Cc. of a solution prepared by dissolving one tablet in 1 Cc. of water, and increasing according to the scale which is being followed. It is to be noted that the last dose with any strength tablet represents the same amount of tuberculin as the first dose with the next higher strength tablet, so that one of these may be omitted.

Table III (Syringe Method).

Prepare a solution in the syringe by dissolving one tablet in 1 Cc. of sterile water in the syringe. Inject the amount indicated.

Column	1	2	3	4	5	6	7	8	9	10	11
Dose 1	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	**0.10**	0.10	0.10
" 2	0.32	0.22	0.18	0.16	0.15	0.14	0.13	0.13	**0.13**	0.12	0.12
" 3	1	0.47	0.32	0.25	0.22	0.20	0.18	0.17	**0.16**	0.15	0.15
" 4		1	0.56	0.40	0.32	0.27	0.24	0.22	**0.20**	0.18	0.18
" 5			1	0.63	0.47	0.37	0.32	0.28	**0.25**	0.23	0.22
" 6				1	0.68	0.52	0.42	0.36	**0.32**	0.29	0.26
" 7					1	0.72	0.56	0.47	**0.40**	0.35	0.32
" 8						1	0.75	0.60	**0.50**	0.43	0.38
" 9								0.77	**0.63**	0.53	0.47
" 10								1	**0.80**	0.66	0.56
" 11									**1**	0.80	0.68
" 12										1	0.83
" 13											1

Column 9 is the scale recommended.

In explanation of this scale of dilutions, it may be pointed out that each of the columns represents a series of doses for conducting the treatment in such a way that the increase in doses is made in a definite ratio. This scale is also sufficiently elastic so that the physician

may increase the dosage very slowly when necessary, or with greater rapidity in cases in which it seems warranted. The various columns of the scale indicate the number of injections employed to carry the treatment from a certain amount to a dose ten times as great. For instance, if column 2 be followed, the treatment is carried from a dose of 1/100,000 mg. to 1/10,000 mg. in four injections.

If column 11 be followed, thirteen doses are employed for the same span.

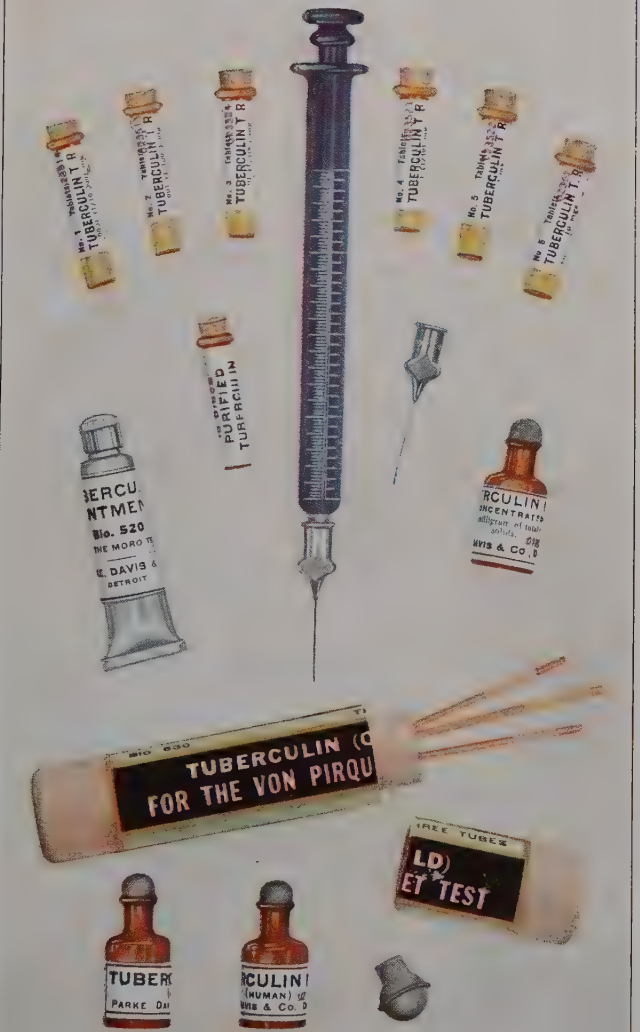
It is suggested that, unless there are indications to the contrary, the outline of doses in column 9 of the scale be followed. This carries the treatment from any dose to one ten times as great in eleven doses and represents a degree of increase which is probably safe in most cases requiring tuberculin treatment.

Table IV (Graduate Method).

Dissolve a tablet in the indicated amount of water and inject 1 Cc. of the solution.

Column	1	2	3	4	5	6	7	8	9	10	11
Dose 1	10	10	10	10	10	10	10	10	**10**	10	10
" 2	3.1	4.5	5.6	6.3	6.7	7.1	7.6	7.7	**7.8**	8.3	8.3
" 3	1	2.1	3.1	4	4.5	5	5.6	5.8	**6.3**	6.7	6.7
" 4		1	1.8	2.5	3.1	3.7	4.2	4.6	**5**	5.6	5.7
" 5			1	1.6	2.1	2.7	3.1	3.8	**4**	4.5	4.7
" 6				1	1.5	1.9	2.3	2.8	**3.1**	3.6	3.8
" 7					1	1.4	1.7	2.2	**2.5**	2.9	3.1
" 8						1	1.3	1.7	**2**	2.4	2.6
" 9							1	1.3	**1.6**	1.9	2.2
" 10								1	**1.3**	1.5	1.8
" 11									**1**	1.2	1.5
" 12										1	1.2
" 13											1

Column 9 indicates the scale of doses recommended.



PARKE, DAVIS & CO. TUBERCULINS

PARKE, DAVIS & CO. VACCINES

In using the Graduate Method of preparing dilutions, the only apparatus required is a sterile 10-Cc. graduate and the ordinary hypodermatic syringe. The tablet is dropped into the graduate and water added as indicated in Table IV. The amount of solution to inject in each case is 1 Cc.

For the first dose, the 1/10,000 tablet is dissolved in 10 Cc. of water, and if the recommended increase in doses be employed (see Table IV) for the second dose a tablet is dissolved in 7.8 Cc., for the third in 6.3 Cc., and so on down the column. In all cases 1 Cc. of the solution is injected. After the doses represented in any column have been given, the treatment is continued with the next strength tablet, that is .001 mg. (1/1000), this being dissolved in 10 Cc. for the first dose of this series, as in the case of the previous series. In the same way as before the scale is followed through the remainder of the series of tablets, 1/100, 1/10, 1 and 10 mg., providing that no marked reactions are elicited. *If, at any time during the treatment, a decided reaction follows an injection, an increase in dosage is contraindicated. All patients do not require the same size doses, nor will they tolerate them.*

TUBERCULIN PACKAGES.

Tuberculin Tablets (both T. R. and B. E.) are supplied in six strengths, ten tablets in a

vial, as follows: .0001 mg. (1/10000 milligram), .001 mg., .01 mg., .1 mg., 1 mg., and 10 mg.—in single vials, and in packages of six vials, Nos. 1 to 6, inclusive.

Other Tuberculins are supplied as follows:

Purified Discs in tubes of 10.

B. E. and T. R. (concentrated liquid) in 1-Cc. glass bulbs, each bulb containing 1 milligram of total dry tubercle solids.

T. R. Dilute in cases of 6 bulbs of 1 Cc. each.

B. F. in 1-Cc. hermetically sealed bulbs, 6 in a box.

Tuberculin Old in ½-Cc. glass bulbs, rubber-stoppered.

Tuberculin Ointment for the Moro Test, in 2-gramme collapsible tubes.

Tuberculin for the von Pirquet Test, three hermetically sealed glass tubes in one package.

Section 9.

ORGANOTHERAPY.

During the last twenty-five years more and more interest has been manifested in the investigation of the functions and diseases of the ductless glands. The importance of these structures has been more generally recognized, and our knowledge of their functions has been largely increased.

We are beginning to learn that many diseases are due to the failure or perversion of normal chemical processes over which the ductless glands have an essential control.

Ductless glands act on other tissues at a distance by means of substances which we name "hormones," these hormones being conveyed by the blood stream to the cells for which they are destined.

The cells of a gland have the property of forming one or more hormones, and each of these hormones has the power of exciting a definite chemical activity in those cells for which it has a special affinity. Substances may be formed which, instead of activating, control or inhibit chemical action. The normal metabolism of the tissues in health is maintained and an adequate supply of hor-

mones is assured by the proper functioning of the ductless glands.

The complex and delicately balanced composition of the blood shows how important this fluid is as a carrier of many vital bodies.

We do not know in what form the hormones are conveyed through the blood stream; whether in solution or suspension in the blood plasma, or attached in some way to the red or white corpuscles. What we do know is that the normal blood carries these hormones efficiently.

The most important ductless glands are the thyroid, parathyroid, pituitary, and suprarenal. Other glands, such as the pancreas and the generative glands, supply both an external and an internal secretion, but in these the two forms of secretion are supplied by two sets of cells, and one set may fail while the other continues active in function.

THYROID.

The effects of disease upon an internal secretion are best observable in the case of the thyroid gland, in which the structure is simple and the secretion can be seen stored in the alveoli of the gland substance. If this gland atrophies, its secretion gradually fails and the symptoms of myxedema slowly develop.

In case of failure of the thyroid gland in man we are able to supply the necessary hor-

mones in an active state from one of the lower animals, and in a measure restore to normal health a person whose thyroid function has been more or less impaired.

Disease is also the result of abnormal activity of the thyroid gland. The secretory activity does not always depend upon the size of the gland. A very great enlargement of the thyroid may take place in some forms of goitre without excessive secretion, whereas in Graves' disease but a slight increase in size may accompany symptoms of active hypersecretion. In Graves' disease certain vital organs are operated at high pressure owing to the excessive thyroid supply, and the symptoms of the disease are the outward expression of this glandular hyperactivity. The respiratory interchange of gases is increased 50 per cent.; sugar toleration is reduced, and glycosuria may occur.

Slight enlargement of the ductless glands may take place in response to special physiological requirements. Thus the pituitary gland enlarges during pregnancy, and the thyroid gland at puberty and during menstruation.

We do not know in what manner the thyroid hormones produce the rapid rhythm of the heart which is so constant a symptom in Graves' disease. The tachycardia is produced in a healthy subject by giving large doses of

thyroid extract, but this does not influence the ventricular rhythm directly.

PARATHYROID.

The true function of the parathyroid glands and their relation to the thyroid itself are little understood. They are generally regarded as separate organs with a special relation to the nervous system, which is shown by the development of tetany when they are removed.

PITUITARY.

The pituitary gland has a remarkable influence upon metabolism.

Disease may be due not only to lack of pituitary hormones, but also to a superabundant supply of these hormones.

SUPRARENAL.

In the suprarenal glands the medulla and cortex have separate functions. The medulla is characterized by the presence of chromatin and is supplying constantly an active hormone, adrenalin. So active is this hormone that one one-thousandth of a milligram per kilogram of body weight suffices to produce a definite rise of blood-pressure; it stimulates the whole of the sympathetic system by its action on the myoneural junction.

We possess in Adrenalin an agent of very great value as a hemostatic, useful also in the treatment of asthma, hay fever, shock and other conditions.

We fully recognize that the ductless glands have important relationships to each other, and that the secretion of one may stimulate or inhibit the activity of the others.

THYREOIDECTIN.

In the preparation of this substance the thyroid gland is removed from the horse by operation, and after a time, when the blood of the animal has become surcharged with the elements normally held in check by the thyroid secretion, the animal is bled and the blood made into Thyreoidectin by desiccation. The theory underlying the use of this product in thyroidism is that the excess of thyroid secretion in the patient's blood will be neutralized by the Thyreoidectin and thus rendered harmless. Before this product was evolved, the milk from thyroidectomized cows and goats had been used in the treatment of exophthalmic goitre with some success.

Therapeutics. Thyreoidectin is indicated in the treatment of pathological conditions attended by hypersecretion of the thyroid gland. Many cases have been reported in which it has controlled the symptoms of exophthalmic goitre in a marked manner. The treatment must be continued for long periods of time to obtain the most favorable results.

Thyreoidectin is supplied in 5-grain capsules, 50 capsules in each bottle.

THYROPROTEIN (BEEBE).

A standardized proteid obtained by a process perfected by S. P. Beebe, Ph.D., M.D., of the Cornell University Medical School, and entrusted to Parke, Davis & Co. by Dr. Beebe, is offered to the medical profession under the name of Thyroprotein (Beebe). It consists of the pure proteids of normal thyroid glands, assayed and adjusted to a definite alkaloidal standard.

Thyroprotein is standardized on the basis of its iodine content, and a uniform intelligible dosage is rendered possible thereby. For the standard we have selected the proteid obtained from normal human thyroid glands. The analyses of this proteid show that one gramme of the purified material contains 3.384 milligrams of iodine. After the purified proteid from the animal glands has been collected its iodine content is determined, and, regardless of whether this proteid is richer or poorer in iodine than the standard, it is considered that each 3.384 milligrams of iodine represents one gramme of the active thyroid proteid.

Therapeutics. Thyroprotein relieves certain disturbances of nutrition, as cretinism and myxedema, in which the thyroid gland is usually found to be undeveloped or atrophied; it

is employed with some success in excessive obesity, keloid, scleroderma, and psoriasis. It has proved of value in some cases of acute mania, melancholia, and puerperal mania, and has been recommended in the early symptoms of eclampsia.

Thyroprotein is supplied in 2-grain tablets containing respectively 1, 2 and 5 per cent. of Thyroprotein. The tablets are put up in bottles of 50. We also market glaseptic ampoules of Thyroprotein, each ampoule containng 1/50 grain in 1 Cc. of physiologic salt soluton. The ampoules are put up in boxes of one dozen.

THYROID GLANDS (DESICCATED).

The fresh thyroid glands of healthy animals are utilized in the manufacture of this product. The investigations made into the physiological action of the thyroid gland seem to indicate that it stimulates the combustion of body-fat and increases the urinary flow; another important effect is the hastening of cell activity. It seems also to prevent the body utilizing all the fat-forming materials which may be ingested.

Therapeutics. This preparation has been successfully used in the treatment of myxedema, and there are few drugs for which as much can be claimed as for thyroids in the relief of the symptoms of this disease. It is also used successfully in the treatment of cretinism, obesity, hemophilia, scleroderma, and

simple goitre. There have been encouraging reports from its use in certain forms of insanity.

Dr. J. F. Percy, of Galesburg, Ill., has treated with thyroid glands (desiccated) cases of nephritis and also cases of nephritis complicated with diabetes mellitus (some thirty-five in all); he states that all the cases were benefited by the treatment, and that none died.

Thyroid Glands (Desiccated) is supplied in powdered form in ounce vials; also in 2-grain capsules, in bottles of 100; and in 1/5-grain, 1-grain and 2-grain tablets, in bottles of 100, 500 and 1000.

THYMUS GLAND (DESICCATED).

The fresh thymus glands of healthy animals are used in the manufacture of this product. The thymus gland has been prescribed quite extensively in certain diseases on the same principle as that governing the use of the thyroid, namely, that it possesses the function of internal secretion and will, therefore, benefit certain systemic conditions in persons in whom the thymus was atrophied too early in life.

Therapeutics. This product has been used with benefit in the treatment of simple and exophthalmic goitre. It has also found use in the treatment of rickets, marasmus, and arthri-

tis deformans. In some cases it acts well when thyroid substance has failed to produce results. It has an advantage over thyroid substance in that there is no risk of producing symptoms of thyroidism by its use.

Dr. S. S. Cohen, of Philadelphia, writing of his experience in the treatment of Graves' disease, says: "On the whole, thymus gland is the most useful of the ductless-gland preparations in the largest number of cases of Graves' disorder. It must be given in sufficient quantity—from 0.5 to 3 grammes (8 to 45 grains) daily—for months together, with the alternate use of adrenalin."

Thymus Glands (Desiccated) is supplied in powdered form, in ounce vials, also in 2-grain capsules in bottles of 100, and chocolate-coated tablets in bottles of 100, 500 and 1000.

ADRENALIN.

"Adrenalin" is the name given by Dr. Jokichi Takamine to the astringent, blood-pressure-raising principle of the adrenals, or suprarenal glands, as first isolated by him and manufactured by Parke, Davis & Co. It is supposed that the chief function of the adrenals is to supply an internal secretion which is responsible for the muscular contractility and preserves the tone of the cardiac and vascular walls, and even of the skeletal muscles. The activity of this secretion is evidently due

to the principle, Adrenalin, which our chemists secure in the form of minute grayish-white crystals.

The literature of Adrenalin has grown to such an extent since the discovery of the product in 1900, and its applications have become so general that justice cannot be done the subject in a work of this kind. Every passing season adds to its wonderful achievements.

Therapeutics. In view of the fact that Adrenalin is not employed (therapeutically) in the crystal form but usually in the form of Adrenalin Chloride Solution, it is understood that wherever the word "Adrenalin" appears (therapeutically speaking) without modification, Adrenalin Chloride Solution, 1:1000, is meant.

Adrenalin is used as an astringent in the treatment of inflamed mucous membranes in any situation. In pathological conditions its use is so very extensive that we can but list the affections in which it has yielded brilliant results: Acne rosacea, angioneurotic edema, antral infection, ascites, asthma, bubonic plague, chloroform narcosis, collapse, conjunctivitis, coryza and rhinitis, dysentery, edema, epistaxis, esophagitis, eye wounds, gastric ulcer, glaucoma, hay fever, hematemesis, hematuria, hemophilia, hemoptysis, hemorrhoids, herpes zoster ophthalmicus, hypertrophied spleen, iritis, keratitis, laryngitis, myocardial insuffi-

ciency, neuralgia, osteomalacia, otitis media, peritonitis, pertussis, opium poisoning, pruritus, purpura fulminans and purpura hemorrhagica, snake-bite, spasmodic croup, stricture, tabes, tonsillitis and hypertrophied tonsils, typhoid fever, urethritis, uterine erosions, varicocele, and vomiting of pregnancy. Also its use in combination with cocaine and novocaine in minor surgery is familiar to every medical student and practitioner. We have prepared a brochure of 135 pages, entitled "Adrenalin, Descriptive and Clinical," containing descriptive matter and clinical reports, a complimentary copy of which will be sent to any physician upon request.

The addition of Adrenalin to cocaine greatly increases the anesthetic effect of the latter. Thus a 0.5 per cent. cocaine and adrenalin solution produces the same anesthetic effect as a 2-per-cent. solution of cocaine alone.

Certain advantages are obtained by combining Adrenalin with novocaine—a synthetic product, which is less toxic than cocaine. It is non-irritant, and possesses the added advantage that it may be repeatedly sterilized, by boiling, without injury. Adrenalin and novocaine combinations may be sterilized, if necessary, by boiling, but the heat should be applied only to as much as is required for immediate use.

Parke, Davis & Co. offer several formulæ of Adrenalin with cocaine, and its substitute

novocaine, for the convenience of the profession, and in such strengths and forms as are most likely to be required. To the solutions of Adrenalin with cocaine and novocaine is added a minute quantity of chloretone to prevent fungoid formation.

Our list of Adrenalin preparations is as follows: Adrenalin Crystals, Adrenalin Chloride Solution, Adrenalin Inhalant, Adrenalin Ointment, Adrenalin Suppositories, Adrenalin Tape (Sterilized), Adrenalin Tablets, Adrenalin Tablets No. 2, Adrenalin and Chloretone Ointment, Adrenalin and Chloretone Suppositories, Adrenalin Compound Suppositories, Adrenalin and Cocaine Tablets, Adrenalin and Cocaine Tablets "B," Adrenalin and Cocaine Tablets "C," Adrenalin and Cocaine Tablets "D," Codrenin "A," Codrenin "B," Codrenin "C," Eudrenin "B," Adrenalin and Eucaine Tablets "B," Adrenalin and Novocaine Tablets, Adrenalin and Novocaine Tablets "B," Adrenalin and Novocaine Tablets "C," Adrenlin and Novocaine Tablets "D," Novrenin, Anesthone Cream, Anesthone Inhalant, and Oral Astringent Lozenges.

SUPRARENAL GLANDS (DESICCATED).

Therapeutics. The results of the internal administration of Suprarenal Glands have been very encouraging in cardiac diseases marked by feeble or irregular pulse, also in Addison's

disease, exophthalmic goitre, rachitis, and simple anemia. Dose, 2 to 4 grains.

Suprarenal Glands, Desiccated, is supplied in powdered form in ounce vials, and in capsules and tablets of 2 grains each, bottles of 100.

SUPRARENAL LIQUID WITH CHLORETONE.

This product is an aqueous extract of suprarenal glands which is physiologically standardized, and preserved with a small amount of chloretone.

Therapeutics. It is intended for application to mucous surfaces, for its astringent and hemostatic effects.

Suprarenal Liquid with Chloretone is supplied in ounce vials.

PITUITRIN (PITUITARY EXTRACT).

Pituitrin is made from the infundibular portion or posterior lobe of the hypophysis. It is standardized by its blood-pressure raising effect. It has a stimulating effect upon the arterial system, the rise of blood-pressure which follows its administration being more protracted than that produced by Adrenalin. It also stimulates unstriated muscle in atonic conditions of uterus, intestine and bladder. Its injection causes neither pain nor local reaction, and no toxic symptoms follow even maximum doses.

Therapeutics. In obstetrics Pituitrin is administered in uterine inertia, postpartum hemorrhage, and after Cæsarian section. It acts within a few minutes, soon attains its maximum effect, and ceases to act after an hour or two; it produces rhythmical uterine contractions, and in the placental period of labor it seems to prevent atony. It is practically impossible to induce abortion or premature labor by means of this agent. In the first stage of labor it stimulates to renewed activity labor pains that have ceased, and it intensifies feeble pains, but its most pronounced action is in the second stage of labor or period of expulsion.

Pituitrin should not be used until the os uteri is well dilated, and never in an obstructed labor.

The post-operative use of Pituitrin is growing in favor with surgeons; post-operative atony of the bladder has been overcome in a large number of gynecological cases by its intramuscular injection. In abdominal surgery the post-operative injection of Pituitrin incites intestinal peristaltic action within one hour, making the patient comfortable by preventing an accumulation of intestinal gases and abdominal distention. Its administration also prevents, in many cases, the post-operative shock of major operations.

Pituitrin has been used with variable success

in the treatment of exophthalmic goitre and cerebral anemia. Good results have also been reported in the control of hemoptysis, epistaxis, and post-operative nasal hemorrhage.

Pituitrin (Pituitary Extract) is supplied in 1-Cc. ampoules, packed six in a box.

CORPORA LUTEA (DESICCATED).

That the generative glands exercise a dual function is generally recognized. The extract of the ovary has been studied clinically for many years and the accepted opinion seems to be that it has undoubted therapeutic value. The corpus luteum contains the principle (hormone) which produces the characteristic effects of ovarian extract, and that the remainder of the organ is of little value therapeutically can hardly be doubted.

To meet the very evident demand for this material we supply the dried and powdered Corpora Lutea. In its preparation we separate the yellow granular material from beef ovaries and discard the remainder of the gland. This granular material is of very delicate structure, and must be handled with the utmost care. It is dried at a low temperature in order that the finished product may possess the maximum therapeutic activity.

As the active principle of the gland has never been separated or identified, it is not possible to standardize the drug for medical

purposes. Close investigation has been made by scientists to determine the difference, if any, in the size and chemical composition of the corpus luteum of ovulation and the corpus luteum of pregnancy.

One of our investigators collected the ovaries from 700 non-pregnant and 689 pregnant cows during the late autumn months, at which time cattle as a rule are in excellent health and all stages of pregnancy are in evidence. The total number of corpora lutea obtained from non-pregnant cows was 316, and from pregnant cows 692. In the pregnant cows one of the ovaries invariably showed a well developed corpus luteum, and less than half of the non-pregnant cows possessed corpora lutea. The color and shape of the two varieties are identical, and it is therefore impossible to make any classification by external appearance only.

To determine the frequency of pregnancy in cattle in the packing-houses, an examination of the ovaries and uteri was made on forty cows appearing consecutively on the killing floors, but of two lots from different sections of the country. These cows were all within the calf-bearing period. Of these forty cows, thirty-five yielded ovaries containing corpora lutea of such size as permitted dissecting out. Of these thirty-five, twenty-nine, or 83 per cent. (72 per cent. of the whole) were pregnant.

The corpora lutea from these pregnant cows were not uniformly large; many were identical in size and appearance with those from non-pregnant animals; others were so large as to occupy five-sixths of the entire ovary.

Owing to the larger yield of corpus luteum from a pound unit of ovaries from pregnant cows than from the same unit of ovaries from non-pregnant cows, the material used in the preparation of Corpora Lutea, P. D. & Co., may run as high as 90 to 95 per cent. of corpus luteum verum.

Therapeutics. Corpora Lutea is used principally to control the symptoms following the removal of the ovaries, and for the relief of the nervous disturbances incidental to the natural menopause. It is also used successfully in dysmenorrhea, amenorrhea, hysteria and neurasthenia. The usual dose is 5 grains, three times a day.

Corpora Lutea is supplied in 5-grain capsules in bottles of 50 and 100, respectively.

* * *

Among the other animal derivatives which are in use to-day are Pepsin, Pancreatin, Ox-gall, and Rennin. We present these in many valuable forms and combinations. Our "pepsin plant" is the largest in the world and our product the finest obtainable in any market.

Section 10.

PARKE, DAVIS & CO.'S BIOLOGICAL FARM.

"From tiny acorns mighty oaks do grow." Twenty years ago Parke, Davis & Co. began the manufacture of biological products. A few rooms, a small stable, and a cinder track to exercise the horses answered the then needs of the Biological Department. The rapid advance into favor and importance of biological therapy cannot be more fully realized than by noting the demands made upon this special department in the matter of equipment.

The biological farm, exceeding in area 700 acres, situated near Rochester, in Oakland County, Mich., U. S. A., 30 miles due north from Detroit, is ideal for the purpose to which it is put.

The topography of the farm, now in its maturity, is gently undulating. It lies at an altitude of about 600 feet above the level of the Detroit River, and is rectangular in shape. Its extreme length from east to west is about one and one-half miles, and its width from north to south about three-quarters of a mile. Its east and west limits are dominated by hills which command to the eye a beautiful pano-

ramic view of the intervening valley. Hills likewise command both the northern and southern limits of the farm, thus enclosing it in a basin of undulating formation. On the southern border, flowing from west to east, is the Clinton River, and about the center of the basin, flowing from north to south and emptying into the Clinton River, is Stony Creek. These streams are fed by living springs, the water being clear and cold.

The soil of the farm in the higher portions consists of a gravel loam mixed with clay, and the meadow or low land is of a sandy loam. The entire tract has been underdrained with tile, thereby insuring the best possible results, and preventing in the low spots standing pools and the breeding of mosquitoes. The slopes of the hilltops are wooded, with clumps of trees here and there along the windings of the creek and the clear-flowing river. The hills, clothed with wood to their crests, appear in abrupt outline from a distance, while the river, the brook, the trees scattered along their banks, and the undulating valley are a delight to behold. The visitor enters the woods, or ascends the higher ground where open vistas through the trees afford the eye many charming views of the valley and the opposite hills. Altogether the farm affords a varied and beautiful prospect.

Of necessity much work of a practical nature

has been done, much is now in the doing, and much yet remains to be accomplished.

Some cereal is produced, and some alfalfa grown, but the main provision of the farm is that of grazing. Here on sunny slopes and in quiet, sheltered nooks, the horses, cattle, sheep and other animals required for the production of the various sera, etc., roam at large under ideal hygienic conditions. The farm, of course, is subdivided by fencing. In each enclosure adequate shelter for the flocks and herds is provided, and in such meadows as are not contiguous to either river or creek the water supply is had from natural springs flowing into solid concrete receptacles.

On the heights, at the western end of the farm, are located the buildings for the clinical work. These constitute at present a group of seven buildings, all of wood and concrete construction, and include an operating building in which the animals are inoculated and bled; a building in which the smallpox vaccine is propagated; another in which the animals are dipped and made thoroughly aseptic preparatory to operative procedure; and three long stables to accommodate the several hundred horses required in this work, together with a building for the breeding and care of the guinea-pigs which are used for test purposes.

This group of buildings constitutes an ideal veterinary institute for the housing of the ani-

mals and for the various operations incidental to the work. To cleanse the buildings, both walls and floors, an adequate supply of water under pressure is instantly available, while at intervals the entire group of buildings is disinfected. Asepsis throughout the whole establishment is rigidly maintained. The operators while on duty wear sterilized duck uniforms, and all instruments and materials are sterilized prior to use.

Located at this plant is a drilled well 300 feet deep which furnishes a sanitary water supply to the various buildings. Artificial heat and electric power are also supplied. A sanitary reduction plant has been fitted up in which animal and vegetable refuse matter is first cooked and then ground for use on the farm as fertilizer.

On the heights at the eastern end of the farm are located the stables for the care and treatment of horses used in the production of Thyreoidectin, with a separate building for surgical work. Here also, somewhat removed from the other buildings, are the detention stables where newly arrived horses are kept for at least two weeks under observation of the chief veterinarian before admission to the general stables.

The entire farm is under the immediate charge of a fully qualified veterinarian, with competent assistants. No expense, no expen-

diture of energy or of time, has been spared, and no detail has been overlooked that mature judgment might foresee would insure ideal working conditions; in short, this farm and its appurtenances constitute a complete scientific equipment for this most important and responsible work.

PARKE, DAVIS & CO.'S RESEARCH LABORATORY.

Recognizing the importance and value of research investigation, Parke, Davis & Co. have built a fireproof building sixty feet wide by one hundred and sixty long, four floors and basement. The building faces directly upon the Detroit River.

This building, as its name indicates, contains the departments engaged in the solution of new problems in chemistry, materia medica and therapeutics, including the special subject of organotherapy. Its investigations extend into the fields of the various sciences related to medicine, and its *personnel* includes specialists in bacteriology, physiology and physiologic chemistry, pharmacology, practical pharmacy, and analytical chemistry. These departments are subdivided into sections, each in charge of an expert in the subject assigned to that section. These include sections on bacteriologic research, physiologic chemistry,

serum research, histologic and pathologic research, chemical and pharmacologic research, the physiologic assay of drugs, and the study of plant bacteriology. There is also here a library numbering more than six thousand volumes pertaining to the sciences of biology, physiology, chemistry, pharmacy, hygiene, sanitation, and general medicine, together with complete files of all the leading periodicals of the world devoted to those sciences, numbering in all about 175 separate publications.

The Parke, Davis & Co. laboratories have received the approval of the Government of the United States, and after rigid official inspection were granted License No. 1 by the Secretary of the Treasury of the United States, under the provisions of the act approved June 1, 1902. As the document has a certain historic interest, we submit a photographic reproduction of the original license.

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